



US011006857B2

(12) **United States Patent**
Parker

(10) **Patent No.:** **US 11,006,857 B2**
(45) **Date of Patent:** **May 18, 2021**

(54) **MOTOR FIBRE NEUROMODULATION**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 172 days.

(21) Appl. No.: **15/574,478**

(22) PCT Filed: **Jun. 1, 2016**

(86) PCT No.: **PCT/AU2016/050439**

§ 371 (c)(1),
(2) Date: **Nov. 15, 2017**

(87) PCT Pub. No.: **WO2016/191815**

PCT Pub. Date: **Dec. 8, 2016**

(65) **Prior Publication Data**

US 2018/0132760 A1 May 17, 2018

(30) **Foreign Application Priority Data**

Jun. 1, 2015 (AU) 2015902393

(51) **Int. Cl.**

A61B 5/11 (2006.01)
A61B 5/04 (2006.01)

(Continued)

(52) **U.S. Cl.**

CPC **A61B 5/1106** (2013.01); **A61B 5/04001** (2013.01); **A61B 5/05** (2013.01);

(Continued)

(58) **Field of Classification Search**

CPC ... **A61B 5/11**; **A61B 5/00**; **A61B 5/04**; **A61B 5/05**; **A61B 5/4887**; **A61B 5/4538**;
(Continued)

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,736,434 A 5/1973 Darrow
3,817,254 A 6/1974 Maurer

(Continued)

FOREIGN PATENT DOCUMENTS

AU 2013277009 B2 1/2016
CN 103648583 A 3/2014

(Continued)

OTHER PUBLICATIONS

International Search Report and Written Opinion for International Application No. PCT/AU2017/050296, Search completed Jul. 28, 2017, dated Jul. 28, 2017, 10 pgs.

(Continued)

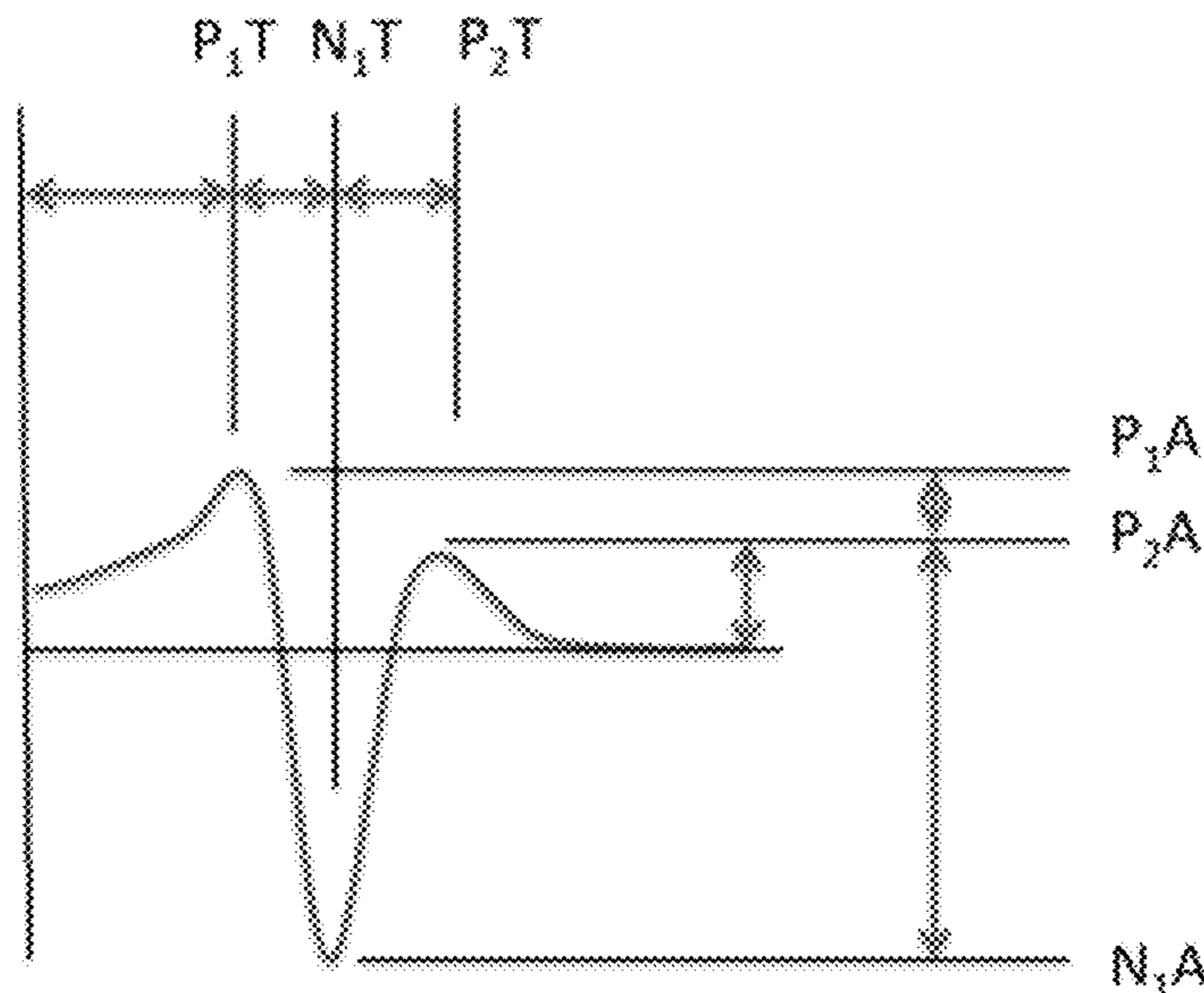
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(57) **ABSTRACT**

A motor response of a muscle to neural stimulation is assessed. Electrical stimuli are applied from a first electrode to a selected neural pathway to evoke an efferent neural response. A slow neural response upon the neural pathway evoked by the electrical stimuli is observed. Based on the slow neural response, a motor response of at least one muscle to the stimuli is assessed.

19 Claims, 7 Drawing Sheets



(51)	Int. Cl.		6,473,649 B1	10/2002	Gryzwa et al.
	<i>A61B 5/00</i>	(2006.01)	6,473,653 B1	10/2002	Schallhorn et al.
	<i>A61N 1/00</i>	(2006.01)	6,493,576 B1	12/2002	Dankwart-Eder
	<i>A61B 5/05</i>	(2021.01)	6,522,932 B1	2/2003	Kuzma
	<i>A61N 1/36</i>	(2006.01)	6,600,955 B1	7/2003	Zierhofer et al.
	<i>A61N 1/20</i>	(2006.01)	6,658,293 B2	12/2003	Vonk et al.
	<i>A61B 5/20</i>	(2006.01)	6,675,046 B2	1/2004	Holsheimer
			6,782,292 B2	8/2004	Whitehurst
			6,898,582 B2	5/2005	Lange et al.
(52)	U.S. Cl.		7,089,059 B1	8/2006	Pless
	CPC	<i>A61B 5/4519</i> (2013.01); <i>A61B 5/4538</i>	7,171,261 B1	1/2007	Litvak et al.
		(2013.01); <i>A61B 5/4887</i> (2013.01); <i>A61N 1/00</i>	7,231,254 B2	6/2007	DiLorenzo et al.
		(2013.01); <i>A61N 1/205</i> (2013.01); <i>A61N</i>	7,286,876 B2	10/2007	Yonce et al.
		<i>1/3605</i> (2013.01); <i>A61N 1/3615</i> (2013.01);	7,412,287 B2	8/2008	Yonce et al.
		<i>A61N 1/36057</i> (2013.01); <i>A61N 1/36135</i>	7,450,992 B1	11/2008	Cameron
		(2013.01); <i>A61B 5/202</i> (2013.01); <i>A61B</i>	7,734,340 B2	6/2010	De Ridder
		<i>5/4052</i> (2013.01); <i>A61B 5/4238</i> (2013.01);	7,742,810 B2	6/2010	Moffitt
		<i>A61B 5/4255</i> (2013.01); <i>A61B 5/4566</i>	7,792,584 B2	9/2010	Van Oort et al.
		(2013.01); <i>A61B 5/4893</i> (2013.01)	7,818,052 B2	10/2010	Litvak et al.
			7,831,305 B2	11/2010	Gliner
			7,835,804 B2	11/2010	Fridman et al.
(58)	Field of Classification Search		7,894,905 B2	2/2011	Pless et al.
	CPC .	<i>A61B 5/04001</i> ; <i>A61B 5/1106</i> ; <i>A61B 5/4519</i> ;	8,190,251 B2	5/2012	Molnar et al.
		<i>A61B 5/4052</i> ; <i>A61B 5/4566</i> ; <i>A61B</i>	8,224,459 B1	7/2012	Pianca et al.
		<i>5/4255</i> ; <i>A61B 5/202</i> ; <i>A61B 5/4238</i> ; <i>A61B</i>	8,239,031 B2	8/2012	Fried et al.
		<i>5/4893</i> ; <i>A61N 1/36</i> ; <i>A61N 1/205</i> ; <i>A61N</i>	8,359,102 B2	1/2013	Thacker et al.
		<i>1/36057</i> ; <i>A61N 1/00</i> ; <i>A61N 1/3605</i> ;	8,417,342 B1*	4/2013	Abell A61N 1/0509
		<i>A61N 1/3615</i> ; <i>A61N 1/36135</i>			607/40
	See application file for complete search history.		8,454,529 B2	6/2013	Daly et al.
			8,494,645 B2	7/2013	Spitzer et al.
			8,588,929 B2	11/2013	Davis et al.
			8,670,830 B2	3/2014	Carlson et al.
			8,886,323 B2	11/2014	Wu et al.
(56)	References Cited		9,155,892 B2	10/2015	Parker et al.
	U.S. PATENT DOCUMENTS		9,302,112 B2	4/2016	Bornzin et al.
			9,381,356 B2	7/2016	Parker et al.
			9,386,934 B2	7/2016	Parker et al.
			9,872,990 B2	1/2018	Parker et al.
			9,974,455 B2	5/2018	Parker et al.
			10,206,596 B2	2/2019	Single et al.
			10,278,600 B2	5/2019	Parker et al.
			10,368,762 B2	8/2019	Single
			10,426,409 B2	10/2019	Single
			10,500,399 B2	12/2019	Single
			10,568,559 B2	2/2020	Parker et al.
			10,588,524 B2	3/2020	Single et al.
			10,588,698 B2	3/2020	Parker et al.
			10,632,307 B2	4/2020	Parker
			10,849,525 B2	12/2020	Parker et al.
			2002/0055688 A1	5/2002	Katims
			2002/0099419 A1	7/2002	Ayal et al.
			2002/0193670 A1	12/2002	Garfield et al.
			2003/0032889 A1	2/2003	Wells
			2003/0045909 A1	3/2003	Gross et al.
			2003/0139781 A1	7/2003	Bradley et al.
			2003/0153959 A1	8/2003	Thacker et al.
			2003/0195580 A1	10/2003	Bradley et al.
			2004/0088017 A1	5/2004	Sharma et al.
			2004/0122482 A1	6/2004	Tung et al.
			2004/0158298 A1	8/2004	Gliner
			2004/0225211 A1	11/2004	Gozani et al.
			2004/0254494 A1	12/2004	Spokoyny et al.
			2005/0010265 A1	1/2005	Baru Fassio
			2005/0017190 A1	1/2005	Eversmann et al.
			2005/0021104 A1	1/2005	DiLorenzo
			2005/0065427 A1	3/2005	Magill
			2005/0070982 A1	3/2005	Heruth et al.
			2005/0075683 A1	4/2005	Miesel et al.
			2005/0101878 A1	5/2005	Daly et al.
			2005/0113877 A1	5/2005	Giardiello et al.
			2005/0137670 A1	6/2005	Christopherson et al.
			2005/0149154 A1	7/2005	Cohen
			2005/0192567 A1	9/2005	Katims
			2005/0203600 A1	9/2005	Wallace
			2005/0209655 A1	9/2005	Bradley et al.
			2005/0282149 A1	12/2005	Kovacs et al.
			2006/0009820 A1	1/2006	Royle et al.
			2006/0020291 A1	1/2006	Gozani
			2006/0135998 A1	6/2006	Libbus et al.

US 11,006,857 B2

(56) **References Cited**

U.S. PATENT DOCUMENTS							
2006/0195159	A1	8/2006	Bradley et al.	2011/0184488	A1	7/2011	De Ridder et al.
2006/0212089	A1	9/2006	Tass	2011/0204811	A1	8/2011	Pollmann-rets
2006/0217782	A1	9/2006	Boveja et al.	2011/0224665	A1*	9/2011	Crosby A61B 18/1492
2006/0264752	A1	11/2006	Rubinsky et al.				606/33
2006/0287609	A1	12/2006	Litvak et al.	2011/0224749	A1	9/2011	Ben-David et al.
2007/0021800	A1	1/2007	Bradley et al.	2011/0264165	A1	10/2011	Molnar et al.
2007/0073354	A1	3/2007	Knudson et al.	2011/0270343	A1	11/2011	Buschman et al.
2007/0100378	A1	5/2007	Maschino	2011/0307030	A1	12/2011	John
2007/0178579	A1	8/2007	Ross et al.	2011/0313310	A1	12/2011	Tomita
2007/0185409	A1	8/2007	Wu et al.	2011/0313483	A1	12/2011	Hincapie et al.
2007/0208394	A1	9/2007	King et al.	2012/0029377	A1	2/2012	Polak
2007/0225767	A1	9/2007	Daly et al.	2012/0059275	A1	3/2012	Fagin et al.
2007/0244410	A1	10/2007	Fridman et al.	2012/0101552	A1	4/2012	Lazarewicz et al.
2007/0250120	A1	10/2007	Flach et al.	2012/0109004	A1	5/2012	Cadwell
2007/0255372	A1	11/2007	Metzler et al.	2012/0109236	A1	5/2012	Jacobson et al.
2007/0282217	A1	12/2007	McGinnis et al.	2012/0155183	A1	6/2012	Aritome
2007/0287931	A1	12/2007	Dilorenzo	2012/0185020	A1	7/2012	Simon et al.
2008/0021292	A1	1/2008	Stypulkowski	2012/0253423	A1	10/2012	Youn et al.
2008/0051647	A1	2/2008	Wu et al.	2012/0277621	A1	11/2012	Gerber et al.
2008/0064947	A1	3/2008	Heruth et al.	2012/0277823	A1	11/2012	Gerber et al.
2008/0077191	A1	3/2008	Morrell	2012/0310301	A1	12/2012	Bennett et al.
2008/0097529	A1	4/2008	Parramon et al.	2012/0310301	A1	12/2012	Bennett et al.
2008/0147155	A1	6/2008	Swoyer	2013/0053722	A1	2/2013	Carlson et al.
2008/0183076	A1	7/2008	Witte et al.	2013/0060302	A1	3/2013	Polefko et al.
2008/0208304	A1	8/2008	Zdravkovic et al.	2013/0172774	A1	7/2013	Crowder et al.
2008/0234780	A1	9/2008	Smith et al.	2013/0289661	A1	10/2013	Griffith et al.
2008/0275527	A1	11/2008	Greenberg et al.	2013/0289683	A1	10/2013	Parker et al.
2008/0294221	A1	11/2008	Kilgore	2014/0066803	A1	3/2014	Choi
2008/0300655	A1	12/2008	Cholette	2014/0142447	A1	5/2014	Takahashi et al.
2008/0319508	A1	12/2008	Botros et al.	2014/0194771	A1	7/2014	Parker et al.
2009/0033486	A1	2/2009	Costantino et al.	2014/0194772	A1	7/2014	Single et al.
2009/0058635	A1	3/2009	Lalonde et al.	2014/0236042	A1	8/2014	Parker et al.
2009/0082691	A1	3/2009	Denison et al.	2014/0236257	A1	8/2014	Parker et al.
2009/0149912	A1*	6/2009	Dacey, Jr. A61N 1/0556 607/45	2014/0243926	A1	8/2014	Carcieri
2009/0157155	A1	6/2009	Bradley	2014/0243931	A1	8/2014	Parker et al.
2009/0270957	A1	10/2009	Pianca	2014/0249396	A1	9/2014	Shacham-diamand et al.
2009/0287277	A1	11/2009	Conn et al.	2014/0276195	A1	9/2014	Papay et al.
2009/0299214	A1	12/2009	Wu et al.	2014/0277250	A1	9/2014	Su et al.
2009/0306491	A1	12/2009	Haggers	2014/0288551	A1	9/2014	Bharmi et al.
2010/0010388	A1	1/2010	Panken et al.	2014/0288577	A1	9/2014	Robinson et al.
2010/0058126	A1	3/2010	Chang et al.	2014/0296737	A1	10/2014	Parker et al.
2010/0069835	A1	3/2010	Parker	2014/0350634	A1	11/2014	Grill et al.
2010/0069996	A1	3/2010	Strahl	2014/0358024	A1	12/2014	Nelson et al.
2010/0070007	A1	3/2010	Parker	2015/0018699	A1	1/2015	Zeng et al.
2010/0070008	A1	3/2010	Parker	2015/0164354	A1	6/2015	Parker et al.
2010/0100153	A1	4/2010	Carlson et al.	2015/0174396	A1	6/2015	Fisher et al.
2010/0106231	A1	4/2010	Torgerson	2015/0238104	A1	8/2015	Tass
2010/0114237	A1	5/2010	Giftakis et al.	2015/0238304	A1	8/2015	Lamraoui
2010/0114258	A1	5/2010	Donofrio et al.	2015/0282725	A1	10/2015	Single
2010/0125313	A1	5/2010	Lee et al.	2015/0313487	A1	11/2015	Single
2010/0125314	A1	5/2010	Bradley et al.	2015/0360031	A1	12/2015	Bornzin et al.
2010/0145222	A1	6/2010	Brunnett et al.	2015/0374999	A1	12/2015	Parker
2010/0152808	A1	6/2010	Boggs	2016/0082265	A1	3/2016	Moffitt et al.
2010/0179626	A1	7/2010	Pilarski	2016/0082268	A1	3/2016	Hershey et al.
2010/0191307	A1	7/2010	Fang et al.	2016/0106980	A1	4/2016	Sürth et al.
2010/0204748	A1	8/2010	Lozano et al.	2016/0121124	A1	5/2016	Johanek et al.
2010/0222844	A1	9/2010	Troosters et al.	2016/0129272	A1*	5/2016	Hou A61N 1/37241
2010/0222858	A1	9/2010	Meloy				607/62
2010/0249643	A1	9/2010	Gozani et al.	2016/0166164	A1	6/2016	Obradovic et al.
2010/0249867	A1	9/2010	Wanasek	2016/0175594	A1*	6/2016	Min A61N 1/3615
2010/0258342	A1	10/2010	Parker				607/62
2010/0262208	A1	10/2010	Parker	2016/0287126	A1	10/2016	Parker et al.
2010/0262214	A1	10/2010	Robinson	2016/0287182	A1	10/2016	Single
2010/0280570	A1	11/2010	Sturm et al.	2016/0367808	A9	12/2016	Simon et al.
2010/0286748	A1	11/2010	Midani et al.	2017/0001017	A9	1/2017	Parker et al.
2010/0331604	A1	12/2010	Okamoto et al.	2017/0049345	A1	2/2017	Single
2010/0331926	A1	12/2010	Lee et al.	2017/0071490	A1	3/2017	Parker et al.
2011/0004207	A1	1/2011	Wallace et al.	2017/0135624	A1	5/2017	Parker
2011/0021943	A1	1/2011	Lacour et al.	2017/0216587	A1	8/2017	Parker
2011/0028859	A1	2/2011	Chian	2017/0361101	A1	12/2017	Single
2011/0040546	A1	2/2011	Gerber et al.	2018/0110987	A1	4/2018	Parker
2011/0087085	A1	4/2011	Tsompazis et al.	2018/0117335	A1	5/2018	Parker et al.
2011/0093042	A1	4/2011	Torgerson et al.	2018/0132747	A1	5/2018	Parker et al.
2011/0106100	A1	5/2011	Bischoff	2018/0133459	A1	5/2018	Parker et al.
				2018/0228391	A1	8/2018	Parker et al.
				2018/0228547	A1	8/2018	Parker
				2018/0229046	A1	8/2018	Parker et al.
				2018/0256052	A1	9/2018	Parker et al.
				2019/0168000	A1	6/2019	Laird-Wah
				2019/0216343	A1	7/2019	Single et al.

(56)

References Cited

U.S. PATENT DOCUMENTS

2019/0239768	A1	8/2019	Karantonis et al.
2019/0307341	A1	10/2019	Parker et al.
2019/0357788	A1	11/2019	Single
2020/0029914	A1	1/2020	Single
2020/0129108	A1	4/2020	Parker et al.
2020/0155240	A1	5/2020	Parker et al.
2020/0215331	A1	7/2020	Single
2020/0282208	A1	9/2020	Parker

FOREIGN PATENT DOCUMENTS

CN	103654762	A	3/2014
CN	103842022	A	6/2014
CN	104411360	A	3/2015
EP	0219084		4/1987
EP	0998958	B1	8/2005
EP	2019716	A	11/2007
EP	2243510	A2	10/2010
EP	2443995	A2	4/2012
EP	2707095	A1	3/2014
EP	3229893	A1	10/2017
JP	2006504494	A	2/2006
JP	2009512505	A	3/2009
JP	2012524629		10/2012
JP	2013527784	A	7/2013
JP	2013536044	A	9/2013
JP	2014522261	A	9/2014
JP	2014523261	A	9/2014
WO	1983003191	A	9/1983
WO	1993001863	A1	2/1993
WO	9612383	A1	4/1996
WO	2000002623	A1	1/2000
WO	2002036003	A1	11/2001
WO	2002038031		5/2002
WO	2002049500	A2	6/2002
WO	2003028521	A2	4/2003
WO	2003043690		5/2003
WO	2003103484		12/2003
WO	2004021885	A1	3/2004
WO	2004103455		12/2004
WO	2005032656	A1	4/2005
WO	2005105202	A1	11/2005
WO	2006091636	A2	8/2006
WO	2007050657	A1	5/2007
WO	2007064936	A1	6/2007
WO	2007127926	A2	11/2007
WO	2007130170	A1	11/2007
WO	2008004204	A1	1/2008
WO	2008049199	A1	5/2008
WO	2009002072	A2	12/2008
WO	2009002579	A1	12/2008
WO	2009010870	A2	1/2009
WO	2009130515	A2	10/2009
WO	2009146427	A1	12/2009
WO	2010013170	A1	2/2010
WO	2010044989	A2	4/2010
WO	2010051392	A1	5/2010
WO	2010057046	A2	5/2010
WO	2010124139	A1	10/2010
WO	2010138915	A1	12/2010
WO	2011011327	A1	1/2011
WO	2011066477	A1	6/2011
WO	2011066478	A1	6/2011
WO	2011112843	A1	9/2011
WO	2011119251	A2	9/2011
WO	2011159545	A2	12/2011
WO	2012027252	A2	3/2012
WO	2012027791	A1	3/2012
WO	2012155183	A1	11/2012
WO	2012155184	A1	11/2012
WO	2012155185	A1	11/2012
WO	2012155187	A1	11/2012
WO	2012155188	A1	11/2012
WO	2012155189	A1	11/2012
WO	2012155190	A1	11/2012

WO	2013063111	A1	5/2013
WO	2013075171	A1	5/2013
WO	2014071445	A1	5/2014
WO	2014071446	A1	5/2014
WO	2014143577	A1	9/2014
WO	2015070281	A1	5/2015
WO	2015074121	A1	5/2015
WO	2015109239	A1	7/2015
WO	2015143509	A1	10/2015
WO	2015168735	A1	11/2015
WO	2016011512		1/2016
WO	2016059556	A1	4/2016
WO	2016077882	A1	5/2016
WO	2016090420	A1	6/2016
WO	2016090436	A1	6/2016
WO	2016115596	A1	7/2016
WO	2016161484	A2	10/2016
WO	2016191807	A1	12/2016
WO	2016191808	A1	12/2016
WO	2016191815	A1	12/2016
WO	2017173493	A1	10/2017
WO	2017219096	A1	12/2017
WO	2019178634	A1	9/2019
WO	2019204884	A1	10/2019

OTHER PUBLICATIONS

- He et al., "Perception threshold and electrode position for spinal cord stimulation", *Pain*, 59 (1994) 55-63 pages.
- Holsheimer et al., "Significance of the Spinal Cord Position in Spinal Cord Stimulation", *Acta Neurochir* (1995) [Suppl] 64: 119-124 pages.
- Holsheimer et al., "Spinal Geometry and Paresthesia Coverage in Spinal Cord Stimulation", (1998 paper) 8 pages.
- Olin et al., "Postural Changes in Spinal Cord Stimulation Perceptual Thresholds", *Neuromodulation*, vol. 1, No. 4, 1998, pp. 171-175.
- Rattay, "Analysis of Models for External Stimulation of Axons", *IEEE Transactions on Biomedical Engineering*, vol. BME-33, No. 10, Oct. 1986, pp. 974-977.
- Ross et al., "Improving Patient Experience with Spinal Cord Stimulation: Implications of Position-Related Changes in Neurostimulation", *Neuromodulation*. 2011; e-pub ahead of print. DOI: 10.1111/j.1525-1403.2011.00407.x 6 pages.
- Struijk, "The Extracellular Potential of a Myelinated Nerve Fiber in an Unbounded Medium and in Nerve Cuff Models", *Biophysical Journal*, vol. 72, Jun. 1997, pp. 2457-2469.
- Gorman et al., "Neural Recordings for Feedback Control of Spinal Cord Stimulation: Reduction of Paresthesia Variability.", 2013, In *International Neuromodulation Society 11th World Congress*. Presented at the International Neuromodulation Society 11th World Congress, Berlin, Germany.
- Hallstrom et al, "Distribution of lumbar spinal evoked potentials and their correlation with stimulation-induced paresthesiae", (1991), *Electroencephalography and clinical neurophysiology* 80:126-139.
- Harper, A. A. et al., "Conduction Velocity is Related to Morphological Cell Type in Rat Dorsal Root Ganglion Neurons", *J. Physiol*, (1985), 359, pp. 31-46.
- Holsheimer et al., "Optimum Electrode Geometry for Spinal Cord Stimulation: the Narrow Bipole and Tripole", *Medical and Biological Engineering and Computing*, 35, No. 5, 1997, pp. 493-497.
- Huff, Terry B. et al., "Real-Time Cars Imaging Reveals a Calpain-Dependent Pathway for Paranodal Myelin Retraction during High-Frequency Stimulation", *PLoS ONE* vol. 6, issue 3 (Mar. 3, 2011): e17176, 11 pgs.
- Kent et al., "Instrumentation to Record Evoked Potentials for Closed-Loop Control of Deep Brain Stimulation", *Conf. Proc. IEEE Eng. Med Biol. Sol*, Aug. 2012, 10 pgs.
- Kent et al., AR, "Recording evoked potentials during deep brain stimulation: development and validation of instrumentation to suppress the stimulus artefact", *J Neural Eng*. Jun. 2012; 9 (3):036004, Apr. 18, 2012. doi: 10.1088/1741-2560/9/3/036004.
- Kim et al., "A Wavelet-Based Method for Action Potential Detection From Extracellular Neural Signal Recording With Low Signal-to-Noise Ratio", *IEEE Transactions on Biomedical Engineering*, vol. 50. No. 8, Aug. 2003.

(56)

References Cited

OTHER PUBLICATIONS

- Kim et al., "Cell Type-specific Changes of the Membrane Properties of Peripherally-axotomized Dorsal Root Ganglion Neurons in a Rat Model of Neuropathic Pain", *Neuroscience* 86, No. 1 (May 21, 1998): 301-309, doi:10.1016/S0306-4522(98)00022-0.
- Krames et al., "Neuromodulation", 1st Edition, Academic Press, 2009, p. 540-541.
- Krarup, Christian, "Compound sensory action potential in normal and pathological human nerves", *Muscle & nerve*, vol. 29, No. 4 (2004), pp. 465-483.
- Krishnan et al., "Excitability Differences in Lower-Limb Motor Axons During and After Ischemia", *Muscle & nerve*, vol. 31, No. 2 (2005), pp. 205-213.
- Kumar et al., "Deep Brain Stimulation for Intractable Pain: a 15-year Experience", *Neurosurgery*, Issue 40, No. 4, Apr. 1997, pp. 736-747.
- Kumar et al., "Double-blind evaluation of subthalamic nucleus deep brain stimulation in advanced Parkinson's disease", by the American Academy of Neurology, 51, No. 3, Sep. 1, 1998, pp. 850-855.
- Kumar et al., "Globus Pallidus Deep Brain Stimulation for Generalized Dystonia: Clinical and PET Investigation", *Neurology*, 53, No. 4, 1999, pp. 871-874.
- Laird et al., "A Model of Evoked Potentials in Spinal Cord Stimulation", *IEEE Engineering in Medicine & Biology Society, 35th Annual Conference*. Osaka, Japan: Jul. 3-7, 2013, pp. 6555-6558.
- Lempka, Scott, "The Electrode-Tissue Interface During Recording and Stimulation in the Central Nervous System", published on May 2010.
- Levy et al., "Incidence and Avoidance of Neurologic Complications with Paddle Type Spinal Cord Stimulation Leads", *Neuromodulation* 14(15), Sep. 2011, pp. 412-422.
- Li et al., S, "Resonant antidromic cortical circuit activation as a consequence of high-frequency subthalamic deep-brain stimulation", *J Neurophysiol*. Dec. 2007; 98(6): 3525-37. First published Oct. 10, 2007. doi:10.1152/jn.00808.2007.
- Ma et al., "Similar Electrophysiological Changes in Axotomized and Neighboring Intact Dorsal Root Ganglion Neurons", *Journal of Neurophysiology* 89, No. 3 (Mar. 1, 2003): 1588-1602, doi:10.1152/jn.00855.2002.
- Macefield, "Spontaneous and Evoked Ectopic Discharges Recorded from Single Human Axons", *Muscle & Nerve* 21, No. 4, Apr. 1998, pp. 461-468.
- Mahnam et al., "Measurement of the current-distance relationship using a novel refractory interaction technique", *J. Neural Eng.* 6(2): 036005, published May 20, 2009, 22 pgs.
- Markandey, Vishal, "ECG Implementation on the TMS320C5515 DSP Medical Development Kit (MDK)", *Texas Instruments Application Report* Jun. 2010, 35 pgs.
- Massachusetts Institute of Techn, "The Compound Action Potential of the Frog Sciatic Nerve", *Quantitative Physiology: Cells and Tissues*. Fall, 1999, Retrieved from <http://umech.mit.edu/freeman/6.021J/2001/lab.pdf> on May 22, 2012.
- Matzner et al., "Na⁺ Conductance and the Threshold for Repetitive Neuronal Firing", *Brain Research* 597, No. 1 (Nov. 27, 1992): 92-98, doi:10.1016/0006-8993(92)91509-D.
- Mcgill, Kevin et al., "On the Nature and Elimination of Stimulus Artifact in Nerve Signals Evoked and Recorded Using Surface Electrodes", *IEEE Transactions on Biomedical Engineering*, vol. BME-29, No. 2, Feb. 1982, pp. 129-137.
- Melzack et al., "Pain mechanisms: a new theory", *Science*, New York, New York, vol. 150, No. 3699, Nov. 19, 1965, pp. 971-979.
- Miles et al., "An Electrode for Prolonged Stimulation of the Brain", *Proc. 8th Meeting World Soc. Stereotactic and Functional Neurosurgery*, Part III, Zurich, 1981, *Appl. Neurophysiol*, 45, 1982, pp. 449-445.
- Misawa et al., "Neuropathic Pain Is Associated with Increased Nodal Persistent Na(+) Currents in Human Diabetic Neuropathy", *Journal of the Peripheral Nervous System: JPNS*, 14, No. 4 (Dec. 2009): 279-284.
- Nordin et al., "Ectopic Sensory Discharges and Paresthesiae in Patients with Disorders of Peripheral Nerves, Dorsal Roots and Dorsal Columns", *Pain* 20, No. 3 (Nov. 1984): 231-245, doi:10.1016/0304-3959(84)90013-7.
- Oakley et al., "Spinal Cord Stimulation: Mechanisms of Action", *Spine* 27, No. 22, Nov. 15, 2002, pp. 2574-2583.
- Oakley et al., "Transverse Tripolar Spinal Cord Stimulation: Results of an International Multicenter Study", *Neuromodulation*, vol. 9, No. 3, 2006, pp. 192-203.
- Obradovic et al., "Effect of pressure on the spinal cord during spinal cord stimulation in an animal model", *Poster, 18th Annual Meeting of the North American Neuromodulation Society*, Dec. 11-14, 2014, Las Vegas.
- Oh et al., "Long-term hardware-related complications of deep brain stimulation", *Neurosurgery*, vol. 50, No. 6, Jun. 2002, pp. 1268-1274, discussion pp. 1274-1276.
- Opsommer, E. et al., "Determination of Nerve Conduction Velocity of C-fibres in Humans from Thermal Thresholds to Contact Heat (Thermode) and from Evoked Brain Potentials to Radiant Heat (CO₂ Laser)", *Neurophysiologie Clinique* 1999, vol. 29, pp. 411-422.
- Orstavik, Kristin et al., "Pathological C-fibres in patients with a chronic painful condition", *Brain* (2003), 126, 567-578.
- Ouyang et al., "Compression Induces Acute Demyelination and Potassium Channel Exposure in Spinal Cord", *Journal of Neurotrauma* 27, No. 6, Jun. 2010, 1109-1120, doi:10.1089/neu.2010.1271.
- Parker et al., "Closing the Loop in Neuromodulation Therapies: Spinal Cord Evoked Compound Action Potentials During Stimulation for Pain Management (230).", 2011, In 15th Annual Meeting, North American Neuromodulation Society (p. 48). Presented at the North American Neuromodulation Society, Las Vegas.
- Parker et al., "Compound Action Potentials Recorded in the Human Spinal Cord During Neurostimulation for Pain Relief", *Pain*, vol. 153, 2012, pp. 593-601.
- Parker et al., "Electrically Evoked Compound Action Potentials Recorded From the Sheep Spinal Cord", *Neuromodulation*, vol. 16, 2013, pp. 295-303.
- Penar et al., "Cortical Evoked Potentials Used for Placement of a Laminotomy Lead Array: A Case Report", *Neuromodulation: Technology at the Neural Interface*, accessed Apr. 19, 2011, doi:10.1111/j.1525-1403.2011.00352.x.
- Richter et al., "EMG and SSEP Monitoring During Cervical Spinal Cord Stimulation", *Journal of Neurosurgical Review* 2011, Southern Academic Press, 1(S1), 2011, pp. 61-63.
- Ridder et al., "Burst Spinal Cord Stimulation for Limb and Back Pain", *World Neurosurgery*, 2013, 9 pgs.
- Ridder et al., "Burst Spinal Cord Stimulation toward Paresthesia-Free Pain Suppression", *May 2010*, vol. 66, pp. 986-990.
- Roy, S. H. et al., "Effects of Electrode Location on Myoelectric Conduction Velocity and Median Frequency Estimates", *J. Appl. Physiol.* 61 (4), 1986, pp. 1510-1517.
- Sayenko et al., "Neuromodulation of evoked muscle potentials induced by epidural spinal-cord stimulation in paralyzed individuals", *Journal of Neurophysiology*, vol. 111, No. 5, 2014, pp. 1088-1099, First published Dec. 11, 2013.
- Schmidt et al., "Gating of tactile input from the hand", *Exp Brain Res*, 1990, 79, pp. 97-102.
- Siegfried et al., "Bilateral Chronic Electrostimulation of Ventroposterolateral Pallidum: A New Therapeutic Approach for Alleviating all Parkinsonian Symptoms", *Neurosurgery*, 35, No. 6, Dec. 1994, pp. 1126-1130.
- Siegfried et al., "Intracerebral Electrode Implantation System", *Journal of Neurosurgery*, vol. 59, No. 2, Aug. 1983, pp. 356-3591.
- Srinivasan, S, "Electrode/Electrolyte Interfaces: Structure and Kinetics of Charge Transfer", *Fuel Cells*, 2006, Chapter 2, 67 Pages.
- Struijk et al., "Paresthesia Thresholds in Spinal Cord Stimulation: A Comparison of Theoretical Results with Clinical Data", *IEEE Transactions on Rehabilitation Engineering*, vol. 1, No. 2, Jun. 1993, pp. 101-108.
- Extended European Search Report for European Application No. 16802237.4, Search completed Dec. 11, 2018, dated Dec. 19, 2018, 9 Pgs.

(56)

References Cited

OTHER PUBLICATIONS

Extended European Search Report for European Application No. 16802238.2, Search completed Oct. 17, 2018, dated Oct. 24, 2018, 8 Pgs.

International Preliminary Report for International Application No. PCT/AU2017/050647, dated Dec. 25, 2018, 8 pgs.

International Search Report and Written Opinion for International Application No. PCT/AU2017/050647, Search completed Sep. 29, 2017, dated Sep. 29, 2017, 13 Pgs.

Partial European Search Report for European Application No. 16775966.1, Search completed Oct. 26, 2018, dated Nov. 6, 2018, 11 Pgs.

Bahmer et al., "Application of triphasic pulses with adjustable phase amplitude ratio (PAR) for cochlear ECAP recording: I. Amplitude growth functions", *Journal of Neuroscience Methods, Clinical Neuroscience*, 2012, vol. 205, pp. 202-211.

Bahmer et al., "Effects of electrical pulse polarity shape on intra cochlear neural responses in humans: Triphasic pulses with cathodic second phase", *Hearing Research*, 2013, vol. 306, pp. 123-130.

Gnadt et al., "Spectral Cancellation of Microstimulation Artifact for Simultaneous Neural Recording In Situ", *IEEE Transactions on Biomedical Engineering*, Oct. 2003, Date of Publication: Sep. 23, 2003, vol. 50, No. 10, pp. 1129-1135, DOI: 10.1109/TBME.2003.816077.

Jeffrey et al., "A reliable method for intracranial electrode implantation and chronic electrical stimulation in the mouse brain", *BMC Neuroscience. Biomed Central. London. GB.* vol. 14. No. 1. Aug. 6, 2013 (Aug. 6, 2013) • p. 82.

Tronnier et al., "Magnetic Resonance Imaging with Implanted Neurostimulators: An In Vitro and In Vivo Study", *Jan. 1999, Neurosurgery*, vol. 44(1), p. 118-125 (Year: 1999).

International Search Report and Written Opinion for International Application No. PCT/AU2016/050430, Search completed Aug. 16, 2016, dated Aug. 16, 2016, 10 Pgs.

International Search Report and Written Opinion for International Application No. PCT/AU2016/050431, Search completed Aug. 16, 2016, dated Aug. 16, 2016, 11 Pgs.

International Search Report and Written Opinion for International Application No. PCT/AU2016/050439, Search completed Jul. 15, 2016, dated Jul. 15, 2016, 8 Pgs.

International Search Report and Written Opinion for International Application No. PCT/AU2015/050215, Search completed Jul. 30, 2015, dated Jul. 30, 2015, 8 Pgs.

International Search Report for Australian Application 2011901829 Search Completed Feb. 6, 2012, dated Feb. 7, 2012, 3pgs.

International Search Report for International Application No. PCT/AU2012/000511, International Filing Date May 11, 2012, Search Completed May 17, 2012, dated May 18, 2012, 4 pgs.

International Search Report for International Application No. PCT/AU2012/000512, International Filing Date May 11, 2012, Search Completed Jul. 10, 2012, dated Jul. 11, 2012, 4 pgs.

International Search Report for International Application No. PCT/AU2012/000513, International Filing Date May 11, 2012, Search Completed May 29, 2012, dated May 30, 2012, 5 pgs.

International Search Report for International Application No. PCT/AU2012/000515, International Filing Date May 11, 2012, Search Completed May 21, 2012, dated Jun. 4, 2012, 5 pgs.

International Search Report for International Application No. PCT/AU2012/000516, International Filing Date May 11, 2012, Search Completed Jul. 11, 2012, dated Jul. 12, 2012, 8 pgs.

International Search Report for International Application No. PCT/AU2012/000517, International Filing Date May 11, 2012, Search Completed Jun. 4, 2012, dated Jun. 6, 2012, 3 pgs.

International Search Report for International Application No. PCT/AU2012/000518, International Filing Date May 11, 2012, Search Completed Jun. 8, 2012, dated Jun. 12, 2012, 4 pgs.

International Type Search Report for International Application No. AU 2015902393, Search completed May 16, 2016, dated May 16, 2016, 8 Pgs.

Medtronic, Spinal Cord Stimulation, RestoreSensor Neurostimulator, Features and Specification: Specification, Printed Jun. 16, 2014, 2 pgs.

Medtronic, Spinal Cord Stimulation, RestoreSensor Neurostimulator, Features and Specification: Summary Printed Jun. 16, 2014, 1 pg.

Written Opinion for International Application No. PCT/AU2012/000511, International Filing Date May 11, 2012, Search Completed May 17, 2012, dated May 18, 2012, 5 pgs.

Written Opinion for International Application No. PCT/AU2012/000512, International Filing Date May 11, 2012, Search Completed Jul. 10, 2012, dated Jul. 11, 2012, 7 pgs.

Written Opinion for International Application No. PCT/AU2012/000513, International Filing Date May 11, 2012, Search Completed May 29, 2012, dated May 30, 2012, 10 pgs.

Written Opinion for International Application No. PCT/AU2012/000515, International Filing Date May 11, 2012, Search Completed May 21, 2012, dated Jun. 4, 2012, 4 pgs.

Written Opinion for International Application No. PCT/AU2012/000516, International Filing Date May 11, 2012, Search Completed Jul. 11, 2012, dated Jul. 12, 2012, 8 pgs.

Written Opinion for International Application No. PCT/AU2012/000517, International Filing Date May 11, 2012, Search Completed Jun. 4, 2012, dated Jun. 6, 2012, 5 pgs.

Written Opinion for International Application No. PCT/AU2012/000518, International Filing Date May 11, 2012, Search Completed Jun. 8, 2012, dated Jun. 12, 2012, 10 pgs.

Medtronic, RestoreSensor Neurostimulator, Retrieved from: <http://web.archive.org/web/20150328092923/http://professional.medtronic.com:80/pt/neuro/scs/prod/restore-sensor/features-specifications/index.htm>, Capture Date Jul. 9, 2012, Printed on May 11, 2017.

"Advanced Pain Therapy using Neurostimulation for Chronic Pain", Medtronic RestoreSensor clinical trial paper, Clinical summary, Nov. 2011, p. 32.

"Battelle Neurotechnology—Moving Beyond the Limits in Neurotechnology", Battelle, www.battelle.org, May 2014, pp. 1-2.

"Haptic technology", Wikipedia, Retrieved from: http://en.wikipedia.org/wiki/Haptic_technology, Last modified on Sep. 15, 2014, Printed on Sep. 15, 2014, 5 pgs.

"Implants for surgery, Cardiac pacemakers", IS-1 standard ISO 5841-3-2000, Oct. 15, 2000.

"Neural Bypass Technology Enables Movement in Paralyzed Patient", Posted on Jul. 29, 2014, 6 a.m. in *Brain chips/computer interface*, pp. 1-2.

"Spinal Cord Stimulation, About Spinal Cord Stimulation", Medtronic, Retrieved from: <http://professional.medtronic.com/pt/neuro/scs/edu/about/index.htm>, Printed on Jun. 16, 2014, 2 pgs.

"Wide bandwidth BioAmplifier", http://www.psyllab.com/html/default_bioamp.htm, Printed Jan. 30, 2014, 1-3 pages.

Alam et al., "Evaluation of optimal electrode configurations for epidural spinal cord stimulation in cervical spinal cord injured rats", *Journal of Neuroscience Methods*, Mar. 2015, 28 pgs.

Andreassen, S. et al., "Muscle Fibre Conduction Velocity in Motor Units of the Human Anterior Tibial Muscle: a New Size Principle Parameter", *J. Physiol.* (1987), 391, pp. 561-571.

Andy, "Parafascicular-Center Median Nuclei Stimulation for Intractable Pain and Dyskinesia (Painful-Dyskinesia)", *Stereotactic and Functional Neurosurgery, Appl. Neurophysiol.*, 43, No. 3-5, 1980, pp. 133-144.

Balzer et al., "Localization of cervical and cervicomedullary stimulation leads for pain treatment using median nerve somatosensory evoked potential collision testing", *Journal of Neurosurgery*, Jan. 2011, vol. 114, No. 1: pp. 200-205.

Blum, A. R., "An Electronic System for Extracellular Neural Stimulation and Recording", Dissertation, Georgia Institute of Technology, Aug. 2007, Retrieved from <http://smartech.gatech.edu/handle/1853/16192> on Jan. 30, 2012.

Borg et al., "Conduction velocity and refractory period of single motor nerve fibres in antecedent poliomyelitis", *Journal of Neurology, Neurosurgery, and Psychiatry*, vol. 50, 1987, 443-446.

Brown et al., "Impact of Deep Brain Stimulation on Upper Limb Askinesia in Parkinson's Disease", *Annals of Neurology*, 45, No. 4, 1999, pp. 473-488.

(56)

References Cited

OTHER PUBLICATIONS

Budagavi et al., "Modelling of compound nerve action potentials health and disease", Engineering in Medicine and Biology Society, 1992 14th Annual International Conference of the IEEE. vol. 6. IEEE, 1992. pp. 2600-2601.

Coquery et al., "Backward and forward masking in the perception of cutaneous stimuli", Perception & Psychophysics, 1973, vol. 13.No. 2, pp. 161-163.

Dawson, G. D., "The relative excitability and conduction velocity of sensory and motor nerve fibres in man", Journal of Physiology, 1956, vol. 131(2), pp. 436-451.

Devergnas et al., A, "Cortical potentials evoked by deep brain stimulation in the subthalamic area", Front Syst Neurosci. 2011; 5: 30. May 13, 2011. doi:10.3389/fnsys.2011.00030.

Dijkstra, E. A., "Ultrasonic Distance Detection for a Closed-Loop Spinal Cord Stimulation System", Proceedings—19th International Conference—IEEE/EMBS Oct. 30-Nov. 2, 1997, Chicago, IL, 4 pgs.

Dillier, N et al., "Measurement of the electrically evoked compound action potential via a neural response telemetry system", Ann. Otol. Rhinol. Laryngol., vol. 111, No. 5, May 2002, pp. 407-414.

Doiron et al., "Persistent Na⁺ Current Modifies Burst Discharge by Regulating Conditional Backpropagation of Dendritic Spikes", Journal of Neurophysiology 89, No. 1 (Jan. 1, 2003): 324-337, doi:10.1152/jn.00729.2002.

England et al., "Increased Numbers of Sodium Channels Form Along Demyelinated Axons", Brain Research 548, No. 1-2 (May 10, 1991): 334-337.

Fagius, J. Et Al., "Sympathetic Reflex Latencies and Conduction Velocities in Normal Man", Journal of Neurological Sciences, 1980, vol. 47, pp. 433-448.

Falowski Et Al., "Spinal Cord Stimulation: an update", Neurotherapeutics: The Journal of the American Society for Experimental NeuroTherapeutics 5, No. 1, Jan. 2008, pp. 86-99.

Fisher, "F-Waves—Physiology and Clinical Uses", The Scientific World Journal, (2007) 7, pp. 144-160.

Franke et al., Felix , "An Online Spike Detection and Spike Classification Algorithm Capable of Instantaneous Resolution of Overlapping Spikes", Journal of Computational Neuroscience, 2010, vol. 29, No. 1-2, pp. 127-148.

Fuentes et al., "Spinal Cord Stimulation Restores Locomotion in Animal Models of Parkinson's Disease", Science, vol. 323, No. 5921, Mar. 20, 2009, pp. 1578-1582.

Gad et al., "Development of a multi-electrode array for spinal cord epidural stimulation to facilitate stepping and standing after a complete spinal cord injury in adult rats", Journal of Neuro Engineering and Rehabilitation 2013, 10:2, 18 pgs.

George et al., "Vagus nerve stimulation: a new tool for brain research and therapy", Biological Psychiatry 47, No. 4, Feb. 15, 2000, pp. 287-295.

Goodall, E. V. , "Modeling Study of Activation and Propagation delays During Stimulation of Peripheral Nerve Fibres with a Tripolar Cuff Electrode", IEEE Transactions on Rehabilitation Engineering, vol. 3, No. 3, Sep. 1995, pp. 272-282.

Gorman et al., "ECAP Mapping of the Spinal Cord: Influence of Electrode Position on A β Recruitment", (2012)., In 16th Annual Meeting. Presented at the North American Neuromodulation Society, Las Vegas, NV.

Extended European Search Report for European Application No. 16739680.3, Search completed Jun. 1, 2018, dated Jun. 12, 2018, 9 Pgs.

European patent application 15861444.6 extended European search report, dated Jul. 23, 2018, 8 pgs.

French et al., "Information transmission at 500 bits/s by action potentials in a mechanosensory neuron of the cockroach", Neuroscience Letters, vol. 243, No. 1-3, Feb. 1, 1998, pp. 113-116.

Herreras, "Local Field Potentials: Myths and Misunderstandings", Frontiers in Neural Circuits, Dec. 15, 2016, vol. 10, Article 1101, 16 pgs.

Struijk et al., "Excitation of Dorsal Root Fibers in Spinal Cord Stimulation: a Theoretical Study", IEEE Transactions on Biomedical Engineering, Jul. 1993, vol. 40, No. 7, pp. 632-639.

Sufka et al., "Gate Control Theory Reconsidered", Brain and Mind, 3, No. 2, 2002, pp. 277-290.

Tamura et al., "Increased Nodal Persistent Na⁺ Currents in Human Neuropathy and Motor Neuron Disease Estimated by Latent Addition", Clinical Neurophysiology 117, No. 11 (Nov. 2006): 2451-2458, doi:10.1016/j.clinph.2006.07.309.

Tasker, "Deep Brain Stimulation is Preferable to Thalamotomy for Tremor Suppression", Surgical Neurology, 49, No. 2, 1998, pp. 145-153.

Taylor et al., "Spinal Cord Stimulation for Chronic Back and Leg Pain and Failed Back Surgery Syndrome: A Systematic Review and Analysis of Prognostic Factors", Spine, vol. 30, No. 1, 2004, pp. 152-160.

Texas Instruments, "Precision, Low Power Instrumentation Amplifiers", Texas Instruments SBOS051B Oct. 1995, Revised Feb. 2005, 20 pgs.

Tomas et al., "Dorsal Root Entry Zone (DREZ) Localization Using Direct Spinal Cord Stimulation Can Improve Results of the DREZ Thermocoagulation Procedure for Intractable Pain Relief", Pain, 2005, vol. 116, pp. 159-163.

Tscherter et al., "Spatiotemporal Characterization of Rhythmic Activity in Rat Spinal Cord Slice Cultures", European Journal of Neuroscience 14, No. 2 (2001), pp. 179-190.

Van Den Berg et al., "Nerve fiber size-related block of action currents by phenytoin in mammalian nerve", Epilepsia, Nov. 1994, 35(6), pp. 1279-1288.

Villavicencio, Alan T., "Laminectomy versus Percutaneous Electrode Placement for Spinal Cord Stimulation," Neurosurgery, vol. 46 (2), Feb. 2000, pp. 399-405.

Vleggeert et al., Lankamp, "Electrophysiology and morphometry of the Aalpha- and Abeta-fiber populations in the normal and regenerating rat sciatic nerve", Experimental Neurology, vol. 187, No. 2, Jun. 1, 2004, Available online Apr. 2, 2004, pp. 337-349.

Woessner, "Blocking Out the Pain, Electric Nerve Block Treatments for Sciatic Neuritis", Retrieved from: <http://www.practicalpainmanagement.com/pain/spine/radiculopathy/blocking-out-pain>, Last updated Jan. 10, 2012.

Wolter et al., "Effects of sub-perception threshold spinal cord stimulation in neuropathic pain: A randomized controlled double-blind crossover study", European Federation of International Association for the Study of Pain Chapters, 2012, pp. 648-655.

Wu et al., "Changes in A β Non-nociceptive Primary Sensory Neurons in a Rat Model of Osteoarthritis Pain", Molecular Pain 6, No. 1 (Jul. 1, 2010): 37, doi:10.1186/1744-8069-6-37.

Xie et al., "Functional Changes in Dorsal Root Ganglion Cells after Chronic Nerve Constriction in the Rat", Journal of Neurophysiology 73, No. 5 (May 1, 1995): 1811-1820.

Xie et al., "Sinusoidal Time-Frequency Wavelet Family and its Application in Electrogastrographic Signal Analysis", Proceedings of the 20th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, vol. 20, No. 3, Oct. 29, 1998, pp. 1450-1453.

Yamada et al., "Extraction and Analysis of the Single Motor Unit F-Wave of the Median Nerve", EMG Methods for Evaluating Muscle and Nerve Function, InTech, 2012, 15 pgs.

Yearwood, T. L., "Pulse Width Programming in Spinal Cord Stimulation: a Clinical Study", Pain Physician. 2010. vol. 13, pp. 321-335.

Yingling et al., "Use of Antidromic Evoked Potentials in Placement of Dorsal Cord Disc Electrodes", Applied Neurophysiology, 1986, vol. 49, pp. 36-41.

Yuan, S. et al., "Recording monophasic action potentials using a platinum-electrode ablation catheter", Europace, Oct. 2000; 2(4):312-319.

European Search Report for European Application 12785619.3 Search Completed Oct. 13, 2014, dated Oct. 23, 2014, 7 pgs.

European Search Report for European Application 12785669.8 Search Completed Sep. 22, 2014, dated Sep. 29, 2014, 5 pgs.

Extended European Search Report for EP Application 12785483.4 completed Sep. 16, 2014, 7 pgs.

(56)

References Cited

OTHER PUBLICATIONS

Extended European Search Report for European Application No. 11820923.8, report completed Dec. 9, 2013, dated Dec. 17, 2013, 6 pgs.

Extended European Search Report for European Application No. 13852669.4, Search completed Jun. 8, 2016, dated Jun. 22, 2016, 09 Pgs.

Extended European Search Report for European Application No. 14861553.7, Search completed Jun. 8 2017, dated Jun. 19, 2017, 8 Pgs.

Extended European Search Report for European Application No. 14863597.2, Search completed Jun. 6, 2017, dated Jun. 13, 2017, 9 Pgs.

Extended European Search Report for European Application No. 15768956.3, Search completed Oct. 3, 2017, dated Oct. 10, 2017, 8 Pgs.

Extended European Search Report for European Application No. 13853514.1, Search completed Jun. 8, 2016, dated Jun. 15, 2016, 07 Pgs.

International Preliminary Report on Patentability for International Application No. PCT/AU2011/001127, dated Mar. 5, 2013, 9 pgs.

International Preliminary Report on Patentability for International Application No. PCT/AU2012/000511, dated Nov. 19, 2013, 6 pgs.

International Preliminary Report on Patentability for International Application No. PCT/AU2012/000512, dated Nov. 19, 2013, 8 pgs.

International Preliminary Report on Patentability for International Application No. PCT/AU2012/000513, dated Nov. 19, 2013, 11 pgs.

International Preliminary Report on Patentability for International Application No. PCT/AU2012/000515, dated Nov. 19, 2013, 5 pgs.

International Preliminary Report on Patentability for International Application No. PCT/AU2012/000516, dated Nov. 19, 2013, 9 pgs.

International Preliminary Report on Patentability for International Application No. PCT/AU2012/000517, dated Nov. 19, 2013, 6 pgs.

International Preliminary Report on Patentability for International Application No. PCT/AU2012/000518, dated Nov. 19, 2013, 11 pgs.

International Preliminary Report on Patentability for International Application No. PCT/AU2012/001441, dated May 27, 2014, 10 pgs.

International Preliminary Report on Patentability for International Application No. PCT/AU2013/001279, dated May 12, 2015, 6 pgs.

International Preliminary Report on Patentability for International Application No. PCT/AU2013/001280, dated May 12, 2015, 6 pgs.

International Preliminary Report on Patentability for International Application No. PCT/AU2014/001049, dated May 17, 2016, 5 pgs.

International Preliminary Report on Patentability for International Application No. PCT/AU2014/050369, dated May 24, 2016, 8 pgs.

International Preliminary Report on Patentability for International Application No. PCT/AU2015/050135, dated Oct. 4, 2016, 13 pgs.

International Preliminary Report on Patentability for International Application No. PCT/AU2015/050215, dated Nov. 8, 2016, 4 pgs.

International Preliminary Report on Patentability for International Application No. PCT/AU2015/050422, dated Jan. 31, 2017, 8 pgs.

International Preliminary Report on Patentability for International Application No. PCT/AU2015/050724, dated May 23, 2017, 5 pgs.

International Preliminary Report on Patentability for International Application No. PCT/AU2015/050753, dated Jun. 13, 2017, 7 pgs.

International Preliminary Report on Patentability for International Application No. PCT/AU2015/050787, dated Jun. 13, 2017, 6 pgs.

International Preliminary Report on Patentability for International Application No. PCT/AU2016/050019, dated Jul. 25, 2017, 9 pgs.

International Preliminary Report on Patentability for International Application No. PCT/AU2016/050263, dated Oct. 10, 2017, 9 pgs.

International Search Report & Written Opinion for International Application No. PCT/AU2013/001280, Search Completed Jan. 16, 2014, dated Jan. 16, 2014, 8 Pgs.

International Search Report and Written Opinion for International Application PCT/AU2013/001279, Search Completed Jan. 9, 2014, dated Jan. 9, 2014, 9 Pgs.

International Search Report and Written Opinion for International Application No. PCT/AU2011/001127, date completed Nov. 11, 2011, dated Nov. 15, 2011, 13 pgs.

International Search Report and Written Opinion for International Application No. PCT/AU2012/001441, International Filing Date Nov. 23, 2012, Search Completed Feb. 26, 2013, dated Feb. 26, 2013, 14 pgs.

International Search Report and Written Opinion for International Application No. PCT/AU2014/001049, Search completed Feb. 10, 2015, dated Feb. 10, 2015, 8 Pgs.

International Search Report and Written Opinion for International Application No. PCT/AU2014/050369, Search completed Feb. 20, 2015, dated Feb. 20, 2015, 14 Pgs.

International Search Report and Written Opinion for International Application No. PCT/AU2015/050135, Search completed Jun. 30, 2015, dated Jun. 30, 2015, 26 Pgs.

International Search Report and Written Opinion for International Application No. PCT/AU2015/050422, Search completed Oct. 14, 2015, dated Oct. 14, 2015, 17 Pgs.

International Search Report and Written Opinion for International Application. No. PCT/AU2015/050724, Search completed May 9, 2016, dated May 9, 2016, 8 Pgs.

International Search Report and Written Opinion for International Application No. PCT/AU2015/050753, Search completed Feb. 10, 2016, dated Feb. 10, 2016, 10 Pgs.

International Search Report and Written Opinion for International Application No. PCT/AU2015/050787, Search completed Mar. 16, 2016, dated Mar. 16, 2016, 10 Pgs.

International Search Report and Written Opinion for International Application No. PCT/AU2016/050019, Search completed May 4, 2016, dated May 4, 2016, 16Pgs.

International Search Report and Written Opinion for International Application No. PCT/AU2016/050263, Search completed Nov. 16, 2016, dated Nov. 16, 2016, 8 Pgs.

Al-Ani et al., "Automatic removal of high-amplitude stimulus artefact from neuronal signal recorded in the subthalamic nucleus", *Journal of Neuroscience Methods*, vol. 198, Issue 1, 2011, pp. 135-146.

Extended European Search Report for European Application No. 17778477.4, report completed Nov. 12, 2019, dated Nov. 20, 2019, 7 pgs.

Extended European Search Report for European Application No. 17814341.8, report completed Dec. 12, 2019, dated Jan. 2, 2020, 8 pgs.

International Preliminary Report on Patentability for International Application No. PCT/AU2018/050278, dated Sep. 29, 2020, 7 pgs.

International Preliminary Report on Patentability for International Application No. PCT/AU2019/050384, dated Oct. 27, 2020, 8 pgs.

International Search Report and Written Opinion for International Application No. PCT/AU2018/050278, Search completed Jun. 18, 2018, dated Jun. 18, 2018, 12 Pgs.

International Search Report and Written Opinion for International Application No. PCT/AU2019/050384, Search completed Jun. 25, 2019, dated Jun. 25, 2019, 15 Pgs.

Japanese Office Action for Application No. 2017-546830, dated Feb. 20, 2020, 5 pages with English translation.

Japanese Office Action for Application No. 2017-553090, dated Mar. 16, 2020, 12 pages with English translation.

Japanese Office Action for Application No. 2018-513699, dated Jun. 8, 2020, 7 pages with English translation.

Office Action for Chinese Patent Application No. 201680020725.4, dated Mar. 16, 2020, 8 pgs.

Kopelman et al., "Attempted Reversible Sympathetic Ganglion Block by an Implantable Neurostimulator", *Interactive CardioVascular and Thoracic Surgery*, Feb. 7, 2012, vol. 14, Issue 5, pp. 605-609, doi:10.1093/icvts/ivr137.

International Preliminary Report for International Application No. PCT/AU2017/050296, dated Oct. 9, 2018, 7 Pgs.

* cited by examiner

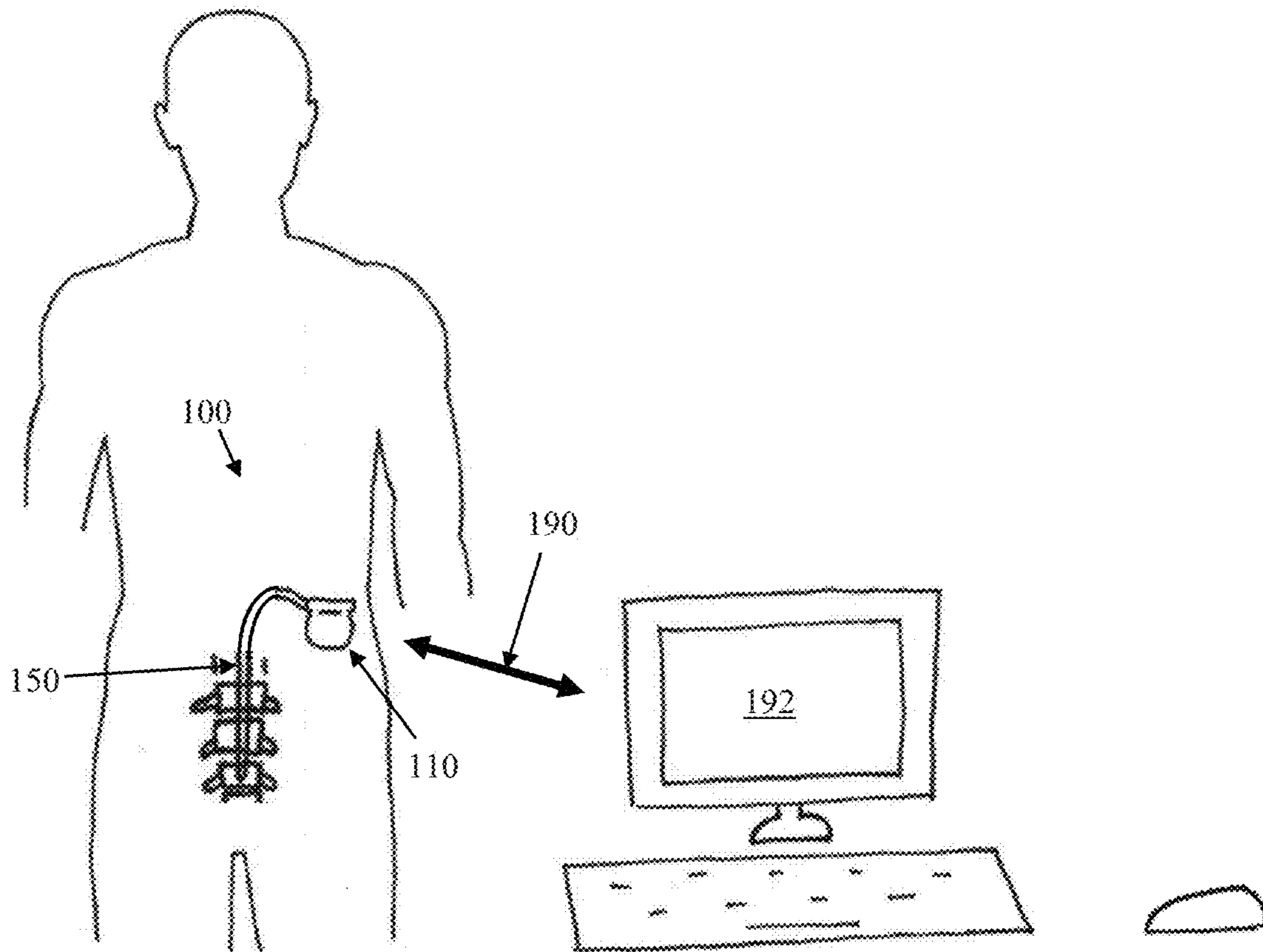


Figure 1

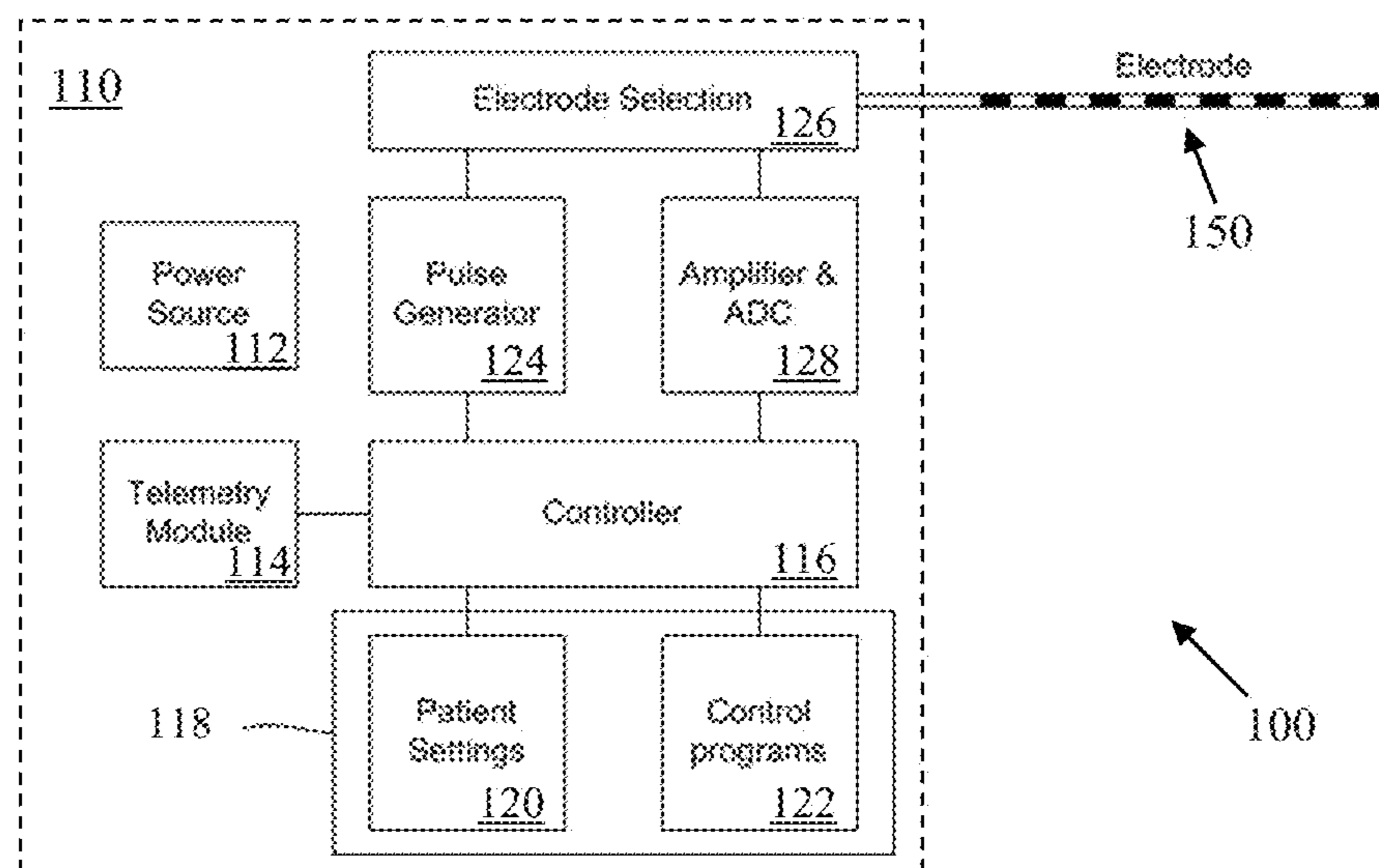


Figure 2

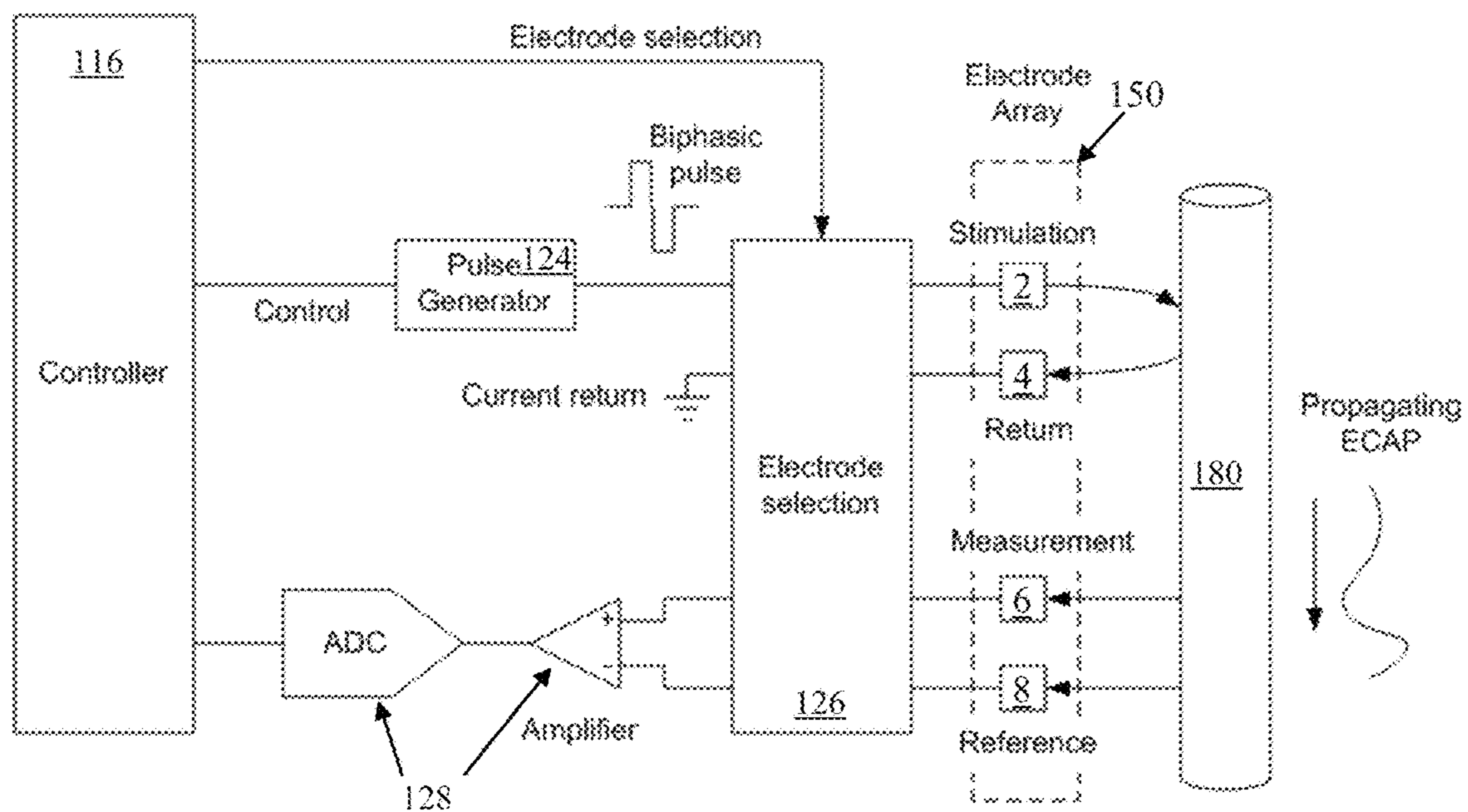


Figure 3

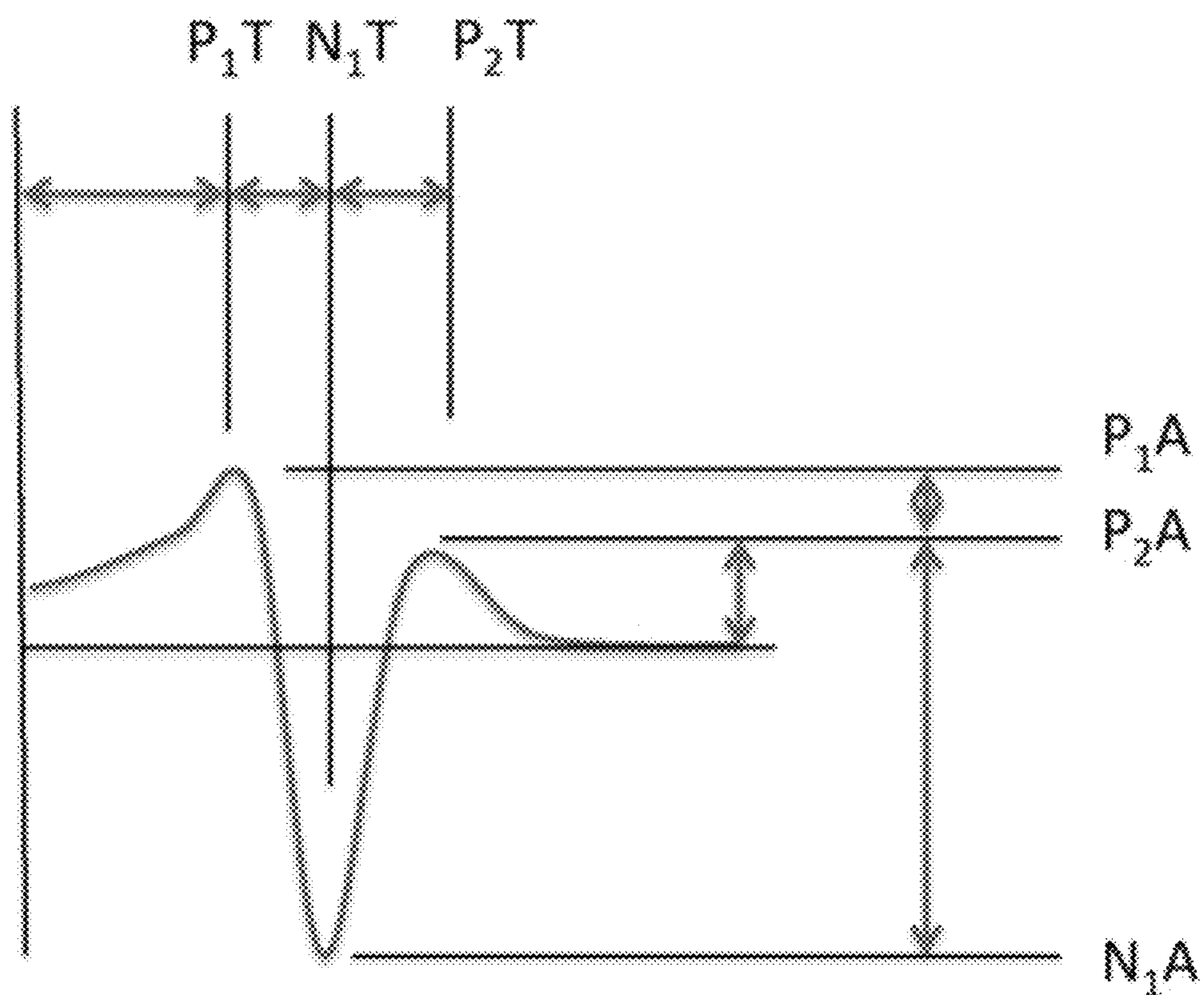


Figure 4

Sheep 7 top of T8 bottom T 13
The reference electrode was posterior

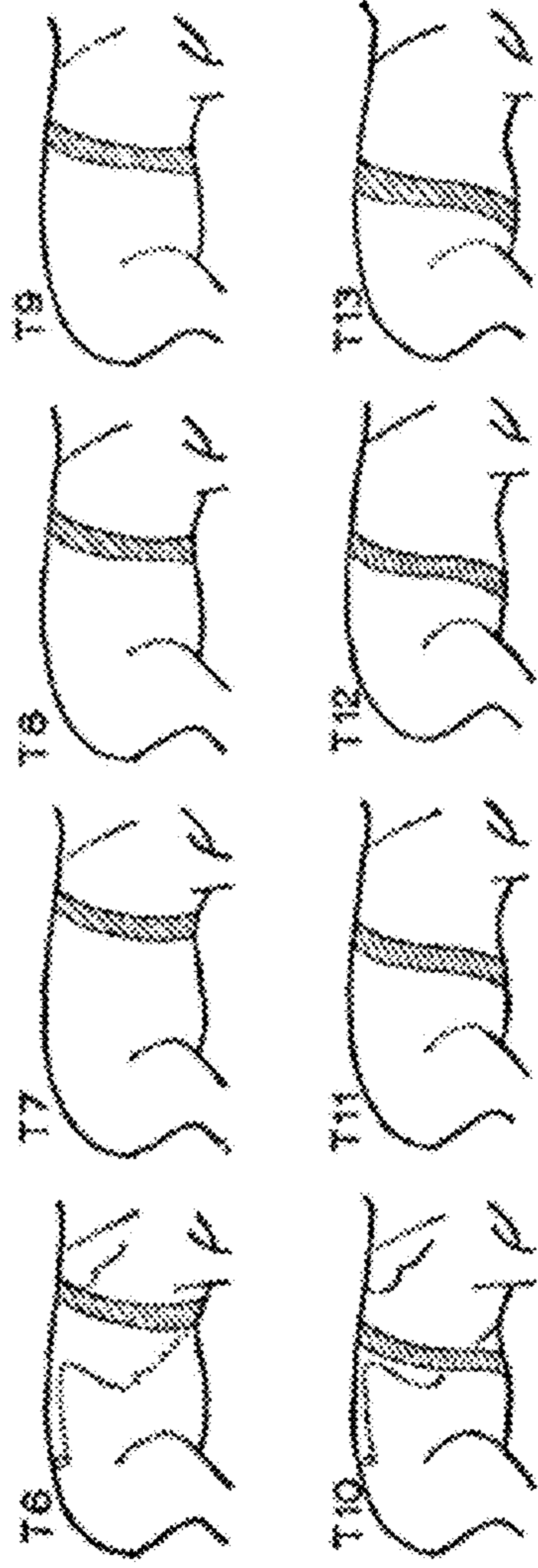
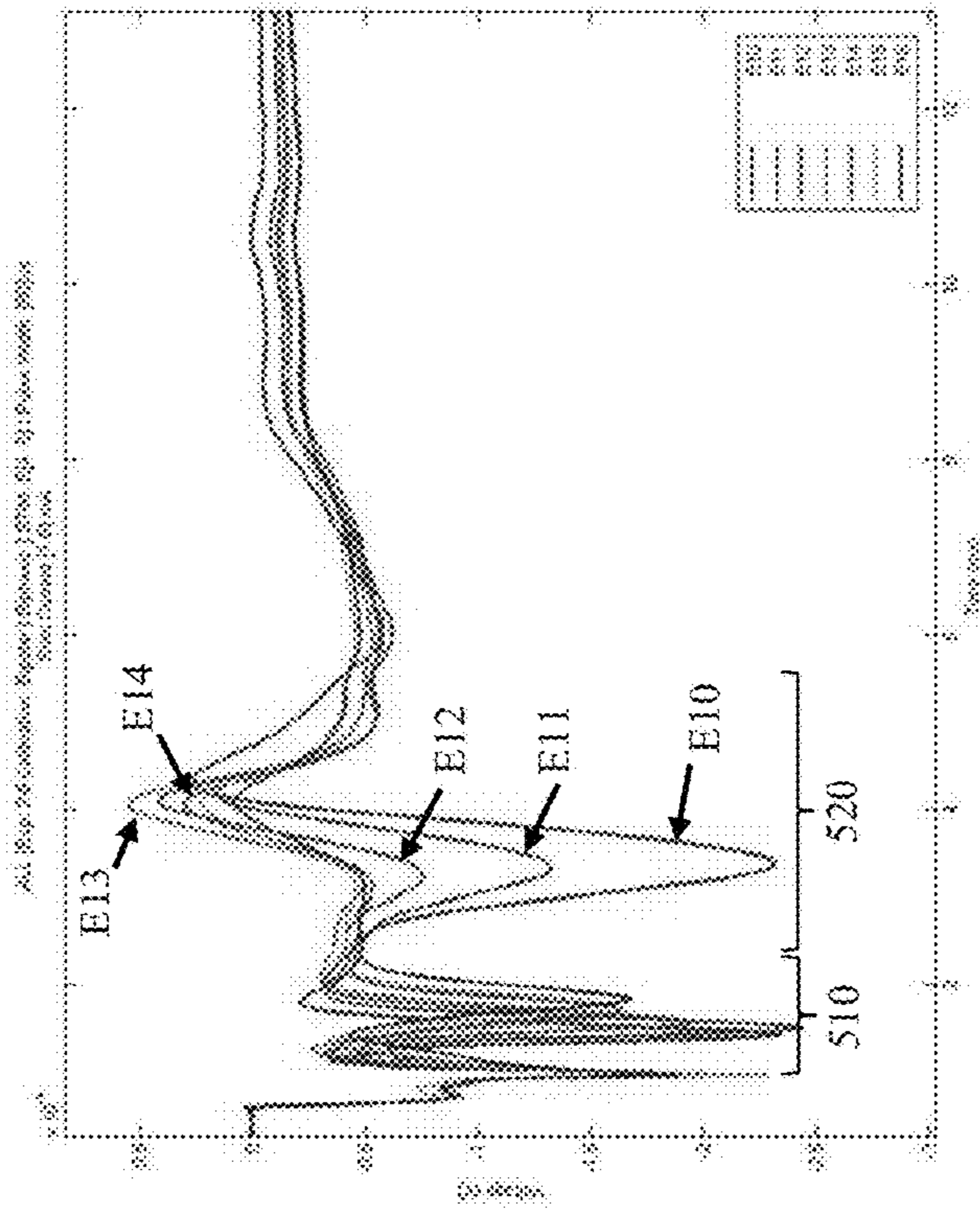
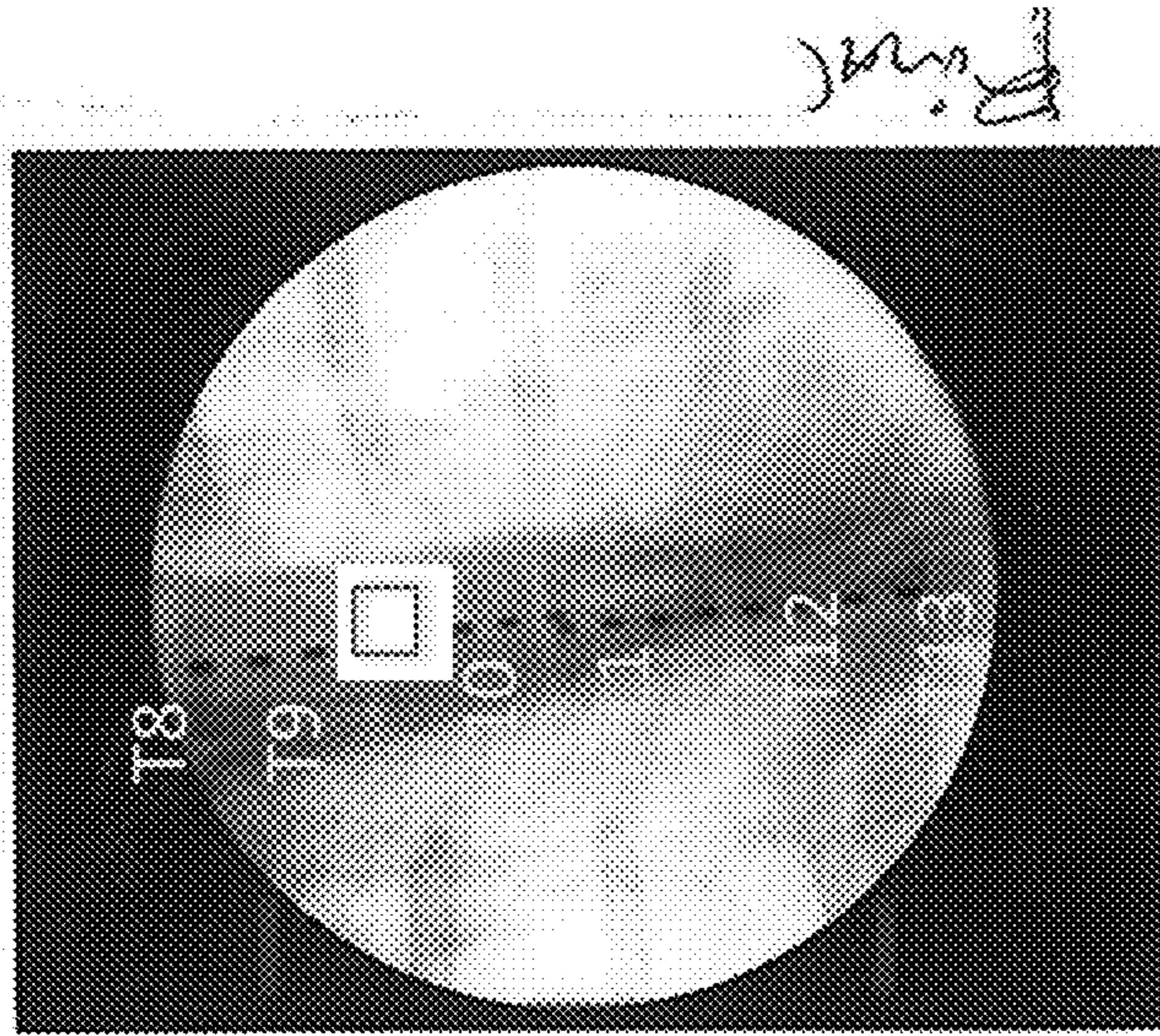
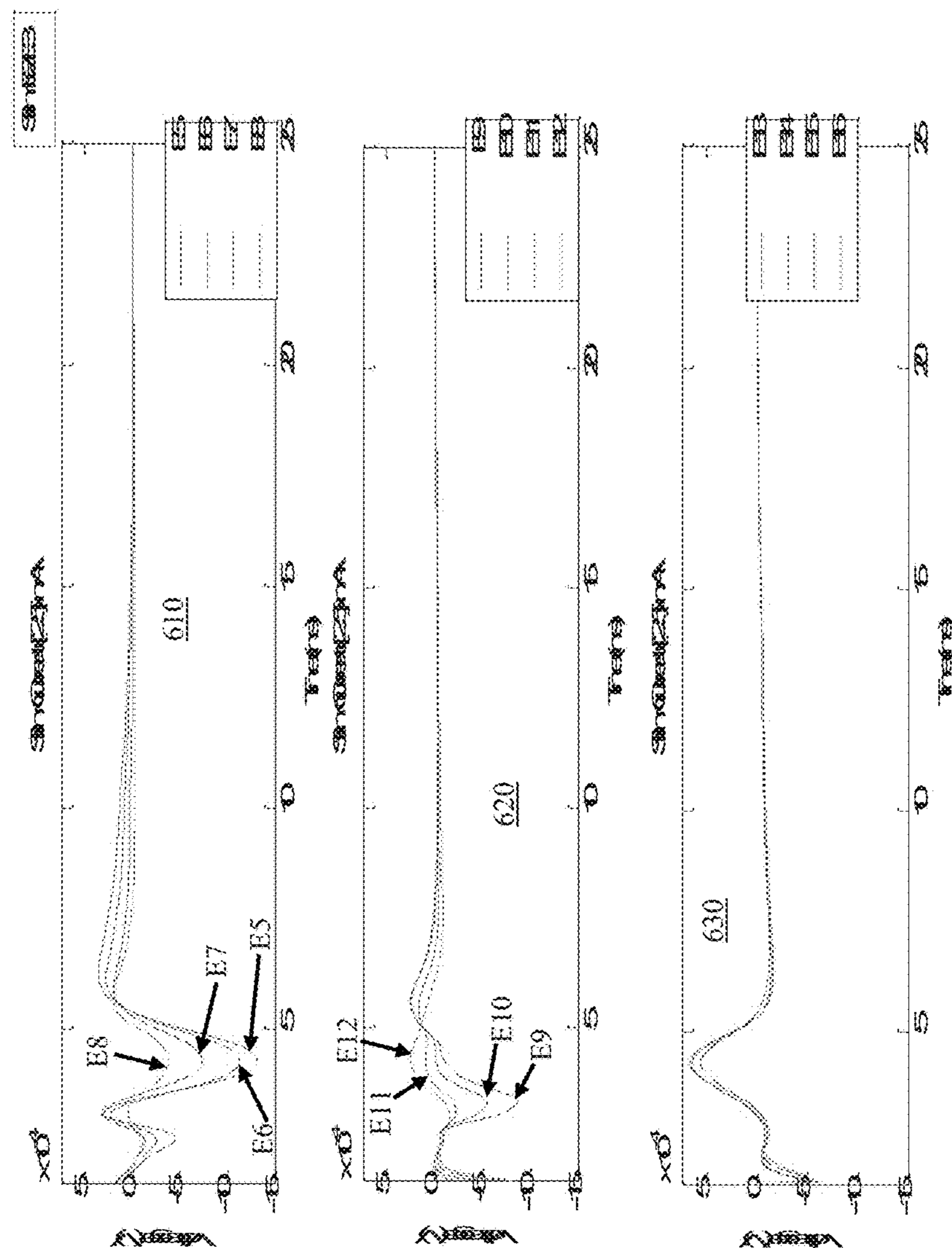


Figure 5

Figure 6



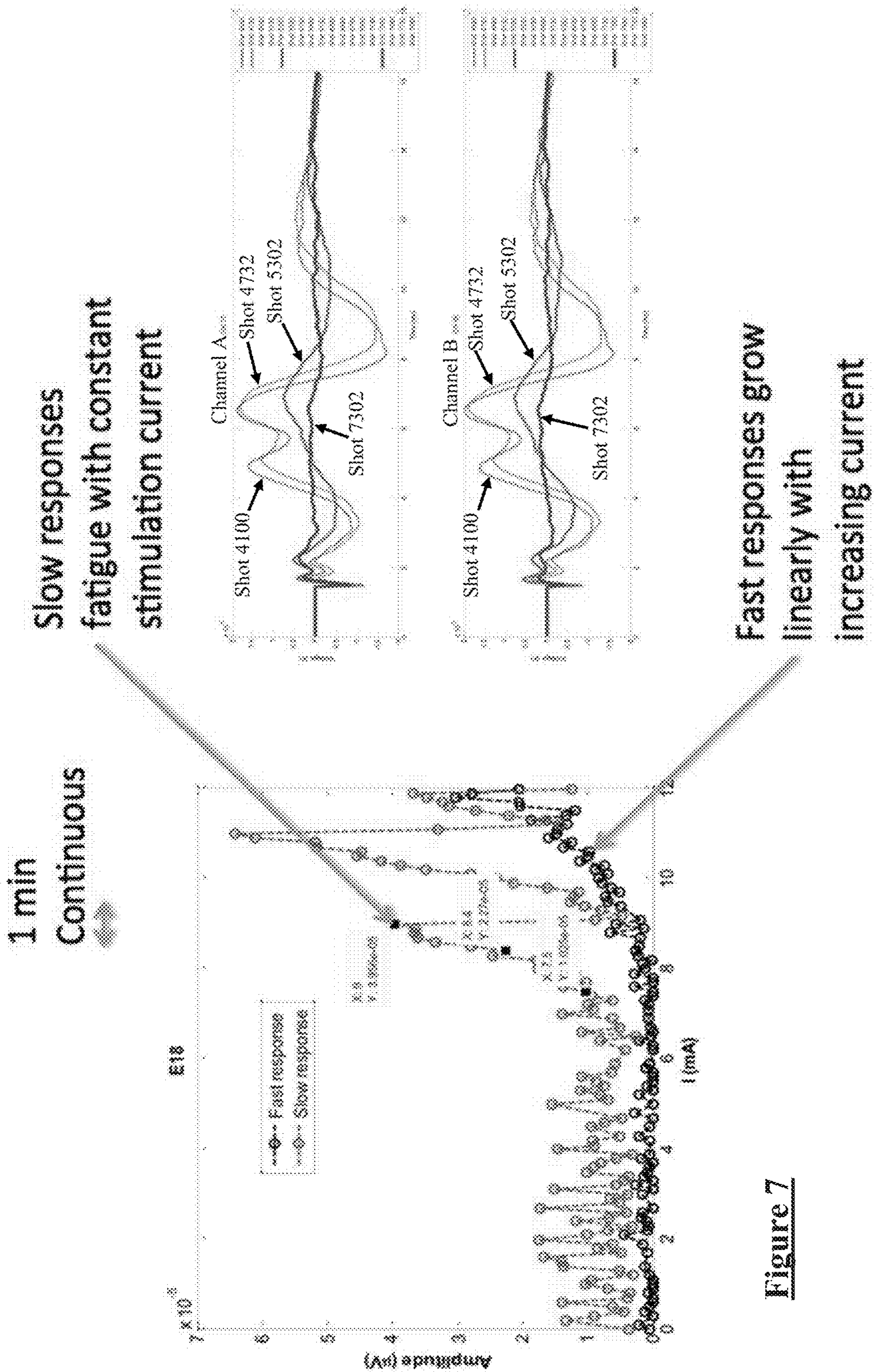


Figure 7

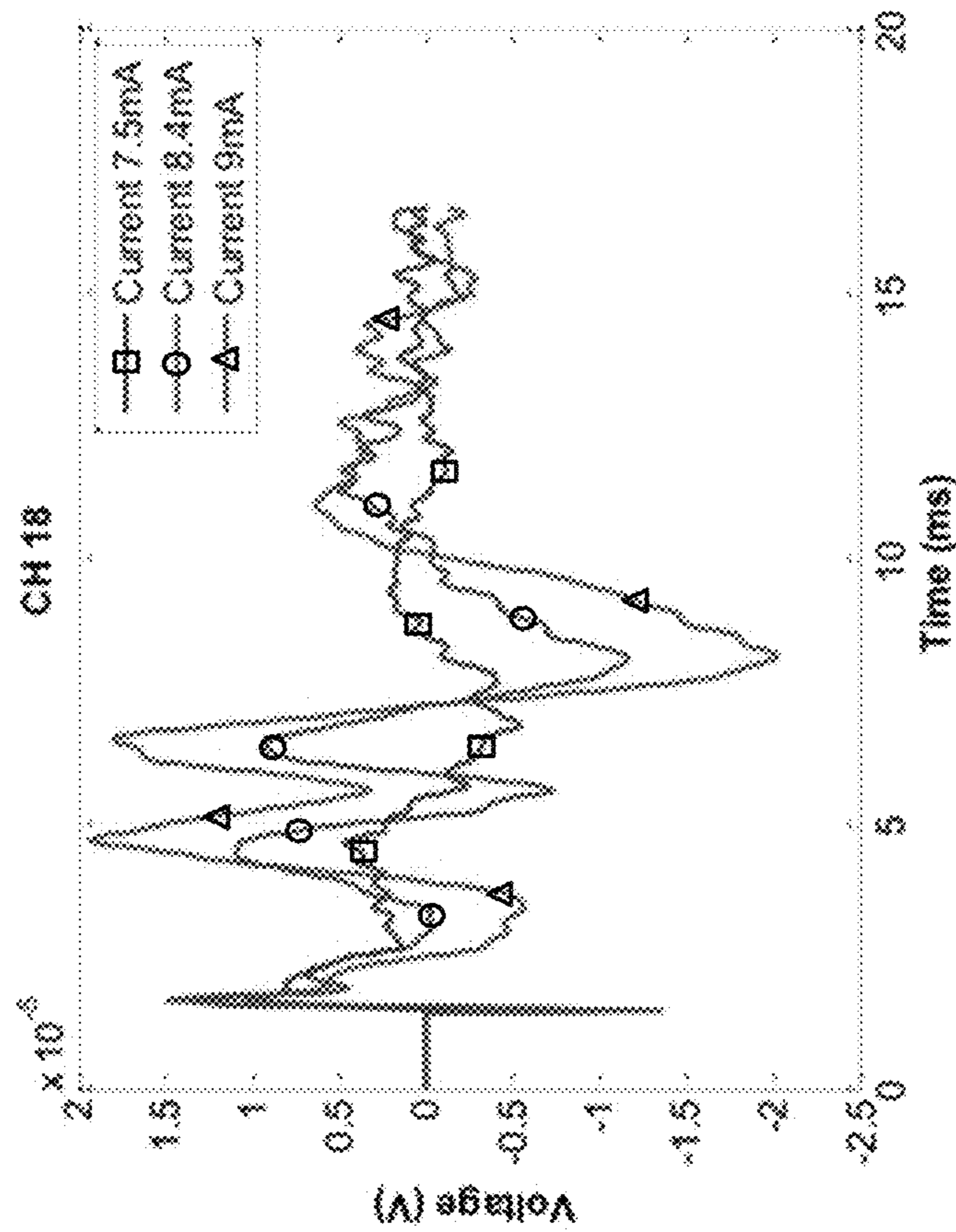
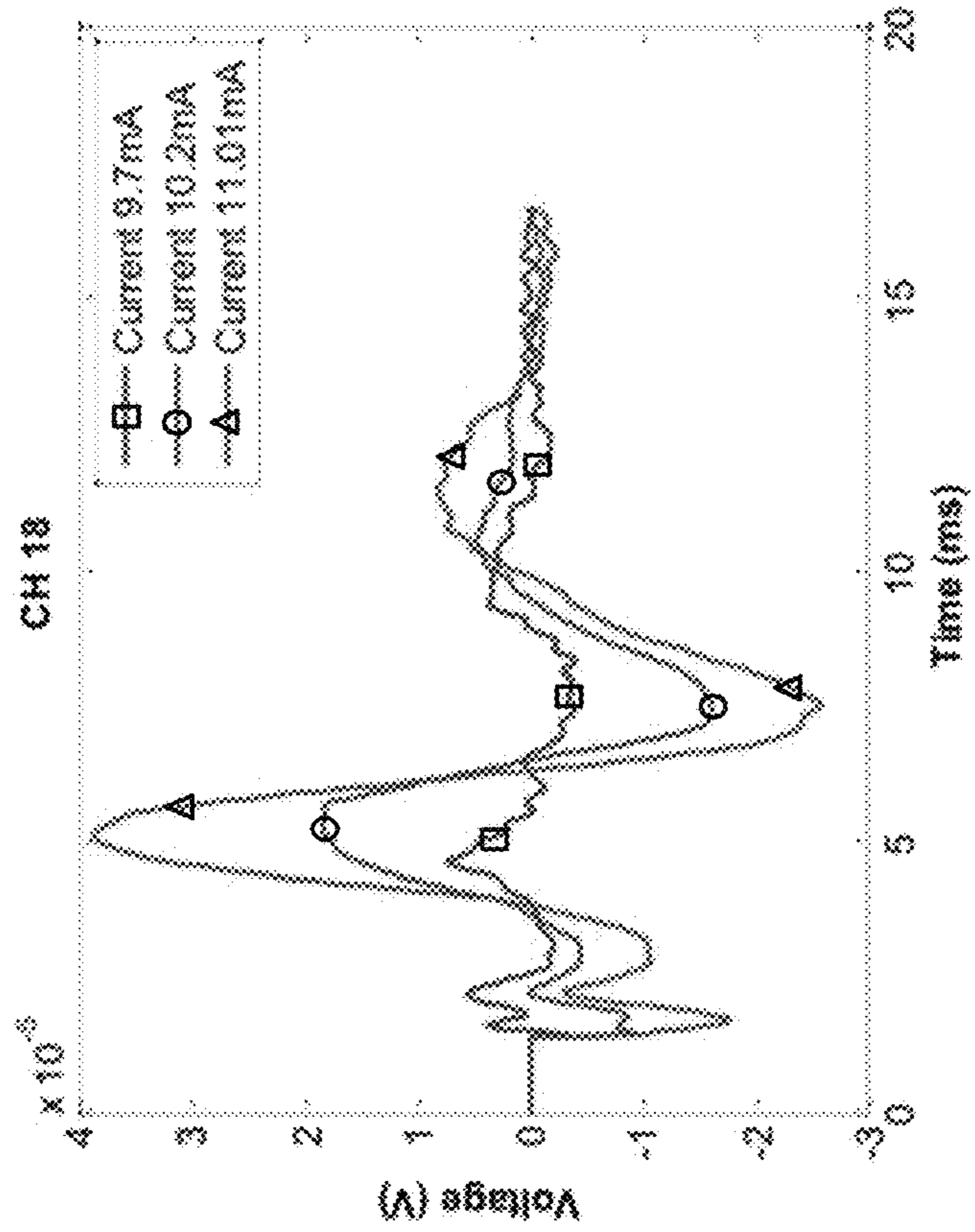


Figure 8

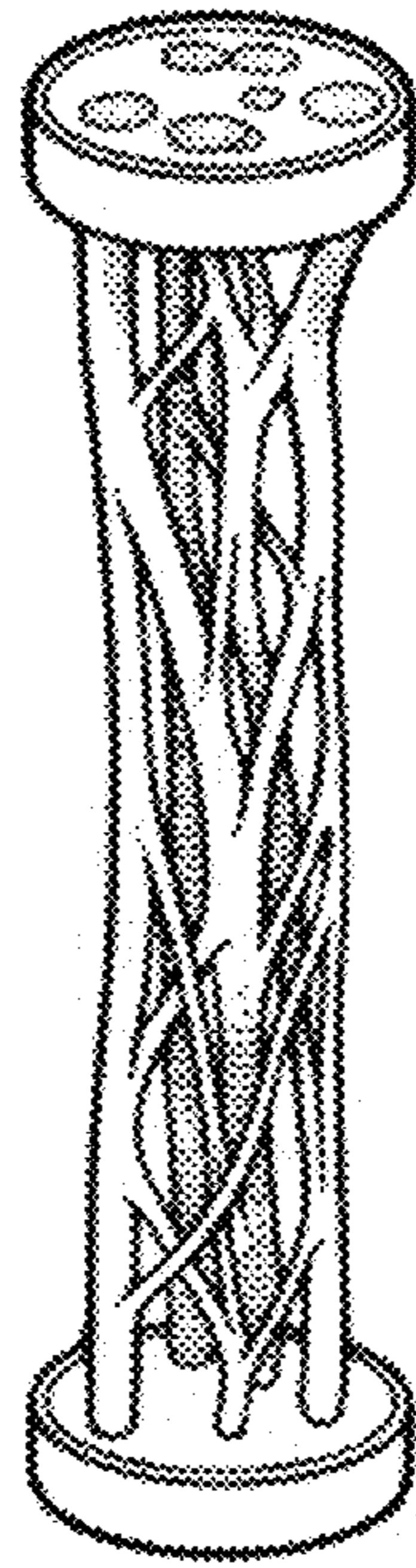


Figure 9

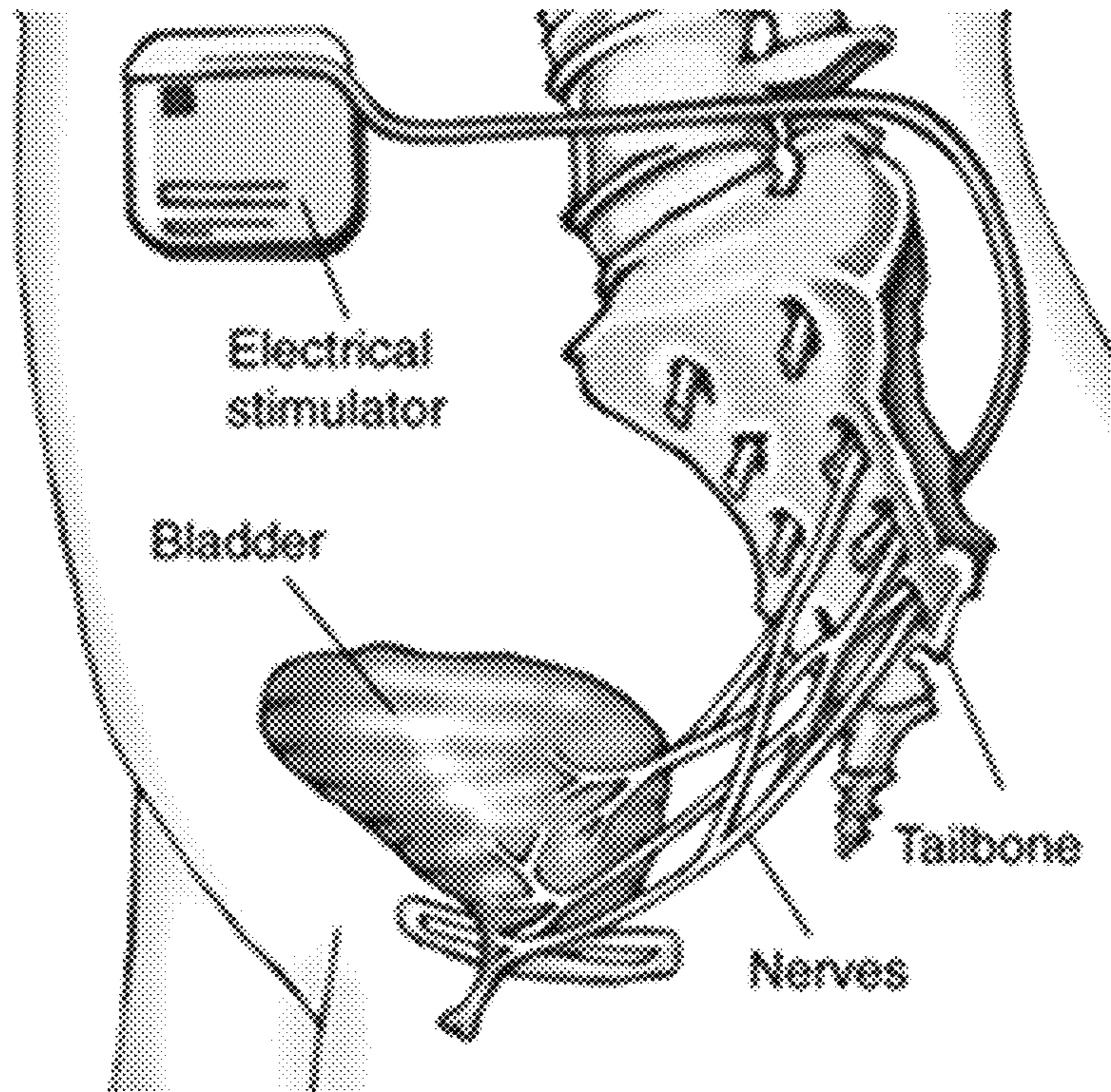


Figure 10

MOTOR FIBRE NEUROMODULATION**CROSS-REFERENCE TO RELATED APPLICATIONS**

This application is a national stage of Application No. PCT/AU2016/050439, filed Jun. 1, 2016, which application claims the benefit of Australian Provisional Patent Application No. 2015902393 filed Jun. 1, 2015, the disclosures of which are incorporated herein by reference in their entireties.

TECHNICAL FIELD

The present invention relates to neuromodulation delivered to motor fibres, and in particular to a method and device for assessing motor fibre and muscle recruitment from neural response measurements.

BACKGROUND OF THE INVENTION

There are a range of situations in which it is desirable to apply neural stimuli in order to give rise to a compound action potential (CAP). A neuromodulation system applies an electrical pulse to tissue in order to generate a therapeutic effect. Such a system typically comprises an implanted electrical pulse generator, and a power source such as a battery that may be rechargeable by transcutaneous inductive transfer. An electrode array is connected to the pulse generator, and is positioned adjacent the target neural pathway(s). An electrical pulse applied to the neural pathway by an electrode causes the depolarisation of neurons, and generation of propagating action potentials. In almost all neuromodulation applications, a single class of fibre response is desired, but the stimulus waveforms employed can recruit action potentials on other classes of fibres which cause unwanted side effects.

Another control problem, facing neuromodulation systems of all types, is achieving neural recruitment at a sufficient level required for therapeutic effect, but at minimal expenditure of energy. The power consumption of the stimulation paradigm has a direct effect on battery requirements which in turn affects the device's physical size and lifetime. For rechargeable systems, increased power consumption results in more frequent charging and, given that batteries only permit a limited number of charging cycles, ultimately this reduces the implanted lifetime of the device.

Neural modulation can be applied to activate a selected muscle group. One example of such neuromodulation is sacral nerve stimulation, in which stimulation frequencies are typically low (<20 Hz) and the currents are usually quite high (up to 7 mA). Without intending to be limited by theory, it is generally thought that sacral nerve stimulation induces a reflex inhibitory effect on the detrusor muscle of the urinary bladder through afferent and efferent fibers in the sacral nerves. Following implantation of a sacral nerve neuromodulator, adjusting the stimulus amplitude and frequency in current stimulation systems is a trial and error procedure. The stimulus amplitude is turned up until a motor response is recorded or the patient informs the programmer that paraesthesias are generated. The amplitude is then reduced below perception threshold and set to that level, but how much reduction is adequate to avoid undesirable motor responses or paraesthesias while still maintaining appropriate therapeutic effect is poorly known.

Any discussion of documents, acts, materials, devices, articles or the like which has been included in the present

specification is solely for the purpose of providing a context for the present invention. It is not to be taken as an admission that any or all of these matters form part of the prior art base or were common general knowledge in the field relevant to the present invention as it existed before the priority date of each claim of this application.

Throughout this specification the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element, integer or step, or group of elements, integers or steps, but not the exclusion of any other element, integer or step, or group of elements, integers or steps.

In this specification, a statement that an element may be "at least one of" a list of options is to be understood that the element may be any one of the listed options, or may be any combination of two or more of the listed options.

SUMMARY OF THE INVENTION

According to a first aspect the present invention provides a method of assessing a motor response to neural stimulation, the method comprising:

applying electrical stimuli from a first electrode to a selected neural pathway to evoke an efferent neural response;

measuring a slow neural response upon the neural pathway evoked by the electrical stimuli;

based on the slow neural response, assessing a motor response of at least one muscle to the stimuli.

According to a second aspect the present invention provides a neurostimulator device comprising:

at least one stimulus electrode configured to be positioned adjacent to a neural pathway and to apply electrical stimuli to the neural pathway to evoke an efferent neural response;

at least one sense electrode configured to be positioned adjacent to the neural pathway and to measure a slow neural response upon the neural pathway evoked by the electrical stimuli; and

a processor for assessing a motor response of at least one muscle to the stimuli, based on the slow neural response.

The present invention further provides computer software, or a computer program product comprising computer program code means, or a non-transitory computer readable medium, or a computing device operating under the control of said software or product, configured to apply electrical stimuli from a first electrode to a selected neural pathway to evoke an efferent neural response, further configured to measure a slow neural response upon the neural pathway evoked by the electrical stimuli, and further configured to assess a motor response of at least one muscle to the stimuli, based on the slow neural response.

Some embodiments of the invention may be applied intra-operatively, in order to use the observed slow response to locate the nerve and optimally position the electrode(s).

Some embodiments of the invention may further comprise applying stimuli at a first level for a period of time sufficient to fatigue a recruited portion of the associated muscle fibre population, and then applying stimuli at an increased level in order to recruit and assess a further portion of the muscle fibre population. Such embodiments may further comprise fatiguing the muscle fibres at various stimulus levels in order to explore characteristics of recruitment of each portion of the muscle fibre population.

Some embodiments may further comprise assessing a pattern or morphology of the slow response, to determine which muscle groups are being recruited by the stimulation.

Preferred embodiments further measure a fast neural response to the stimuli. The fast response may be defined as the neural response observed in a time period of 0-2 ms or 0-2.5 ms after a stimulus. The slow response may in some embodiments comprise the neural response observed during a time period of 2-15 ms after a stimulus, or 2.5-8 ms after a stimulus.

In some embodiments the stimulus is applied to preferentially evoke motor responses whether to stimulate motor activity or suppress motor activity. Thus it is to be appreciated that the motor response of the at least one muscle to the stimuli assessed by the present invention could comprise either or both of an increase in or commencement of a muscle response, or a reduction in or absence of a muscle response.

It is to be noted that a muscle fibre or group may be innervated by multiple nerves, and the "neural pathway" is defined herein to encompass such situations. In particular, in some embodiments the evoked efferent neural response may arise on one nerve innervating the muscle, while the late response may be observed on another nerve which is associated with the same muscle and which carries the or a late response returned from the muscle. For example, stimulation may be applied to a neural pathway on a first side of the body, and the late response may be observed upon a neural pathway on a contralateral second side of the body.

In some embodiments, the neural pathway comprises the sacral nerve. The muscle may comprise the detrusor muscle.

In some embodiments, the neural pathway is used for gastric pacing, and the muscle comprises a gastric muscle.

In some embodiments, the neural pathway is used for functional electrical stimulation (FES).

In some embodiments, the neural pathway is used for multifidus pacing, and the muscle comprises the multifidus.

BRIEF DESCRIPTION OF THE DRAWINGS

An example of the invention will now be described with reference to the accompanying drawings, in which:

FIG. 1 schematically illustrates an implanted sacral nerve stimulator;

FIG. 2 is a block diagram of the implanted neurostimulator;

FIG. 3 is a schematic illustrating interaction of the implanted stimulator with a nerve;

FIG. 4 illustrates the typical form of an electrically evoked compound action potential (ECAP) of a healthy subject;

FIG. 5 shows fast and slow responses obtained from the sheep spinal cord;

FIG. 6 is a plot of fast responses and slow responses arising from stimulation;

FIG. 7 shows fatigue in the amplitude of slow responses;

FIG. 8 shows that slow responses have a different morphology in different portions of the muscle fibre population;

FIG. 9 illustrates nerve fascicle distribution in a nerve fibre bundle; and

FIG. 10 shows the anatomy of sacral nerve stimulation for bladder control.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

FIG. 1 schematically illustrates an implanted sacral nerve stimulator 100. Stimulator 100 comprises an electronics module 110 implanted at a suitable location in the patient's lower abdominal area or posterior superior gluteal region,

and an electrode assembly 150 implanted within the sacrum and connected to the module 110 by a suitable lead. Numerous aspects of operation of implanted neural device 100 are reconfigurable by an external control device 192. Moreover, implanted neural device 100 serves a data gathering role, with gathered data being communicated to external device 192.

FIG. 2 is a block diagram of the implanted neurostimulator 100. Module 110 contains a battery 112 and a telemetry module 114. In embodiments of the present invention, any suitable type of transcutaneous communication 190, such as infrared (IR), electromagnetic, capacitive and inductive transfer, may be used by telemetry module 114 to transfer power and/or data between an external device 192 and the electronics module 110.

Module controller 116 has an associated memory 118 storing patient settings 120, control programs 122 and the like. Controller 116 controls a pulse generator 124 to generate stimuli in the form of current pulses in accordance with the patient settings 120 and control programs 122. Electrode selection module 126 switches the generated pulses to the appropriate electrode(s) of electrode array 150, for delivery of the current pulse to the tissue surrounding the selected electrode(s). Other electrode arrays may also be provided and may be similarly addressed by electrode selection module 126, for example as in the case of FIGS. 5 and 6, discussed further below. Measurement circuitry 128 is configured to capture measurements of neural responses sensed at sense electrode(s) of the electrode array as selected by electrode selection module 126.

FIG. 3 is a schematic illustrating interaction of the implanted stimulator 100 with a nerve 180, in this case the sacral nerve however alternative embodiments may be positioned adjacent any desired neural tissue including a peripheral nerve, visceral nerve, parasympathetic nerve or a brain structure. Electrode selection module 126 selects a stimulation electrode 2 of electrode array 150 to deliver an electrical current pulse to surrounding tissue including nerve 180, and also selects a return electrode 4 of the array 150 for stimulus current recovery to maintain a zero net charge transfer.

Delivery of an appropriate stimulus to the nerve 180 evokes a neural response comprising a compound action potential which will propagate along the nerve 180 as illustrated, for therapeutic purposes which in the case of a sacral nerve stimulator might be to stimulate motor function of desired muscle fibres of the detrusor. To this end the stimulus electrodes are used to deliver stimuli at <20 Hz.

The device 100 is further configured to sense the existence and intensity of compound action potentials (CAPs) propagating along nerve 180, whether such CAPs are evoked by the stimulus from electrodes 2 and 4, or otherwise evoked. To this end, any electrodes of the array 150 may be selected by the electrode selection module 126 to serve as measurement electrode 6 and measurement reference electrode 8. Signals sensed by the measurement electrodes 6 and 8 are passed to measurement circuitry 128, which for example may operate in accordance with the teachings of International Patent Application Publication No. WO2012155183 by the present applicant, the content of which is incorporated herein by reference.

FIG. 4 illustrates the typical form of an electrically evoked compound action potential (ECAP) of a healthy subject. The shape and duration of the compound action potential shown in FIG. 4 is predictable because it is a result of the ion currents produced by the ensemble of axons generating action potentials in response to stimulation. The action potentials generated among a large number of fibres

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sum to form a compound action potential (CAP). The CAP is the sum of responses from a large number of single fibre action potentials. The CAP recorded is the result of a large number of different fibres depolarising. The propagation velocity of the action potential on each fibre is determined largely by the diameter of that fibre. The CAP generated from the firing of a group of similar fibres is measured as a positive peak potential P1, then a negative peak N1, followed by a second positive peak P2. This is caused by the region of activation passing the recording electrode as the action potentials propagate along the individual fibres. An observed electrically evoked CAP signal will typically have a maximum amplitude in the range of microvolts and a duration of 2-3 ms.

The CAP profile takes a typical form and can be characterised by any suitable parameter(s) of which some are indicated in FIG. 4. Depending on the polarity of recording, a normal recorded profile may take an inverse form to that shown in FIG. 4, i.e. having two negative peaks N1 and N2, and one positive peak P1.

The present embodiment recognises that neural responses measured on the sacral nerve 180 not only provide the information shown in FIG. 4, but also at a later time reveal information about the evoked motor response. That is, ECAP recordings from the sacral nerve demonstrate both fast and slow responses. The fast responses are as shown in FIG. 4 and are the result of stimulation of large diameter A β fibres in the nerve bundle. The slower responses occur in the timeframe of about 2.5-7 ms after delivery of a stimulus and, without intending to be limited by theory, are thought to be due to the activation of a muscle group through either direct stimulation of the motor fibre or through activation of the spinal reflex arc. Slow responses are consistent with the theory above i.e. sacral neuromodulation activates a muscle presumably the detrusor. The present invention recognizes that it is further possible to determine which muscle groups are recruited from the pattern of the slow response.

To this end, slow responses have been measured experimentally from the sheep spinal cord and it has been noted that there are differences in the responses observed, depending on the origin of the response. FIG. 5 shows both fast 510 and slow 520 propagating neural responses from the sheep spinal cord. The Xray in FIG. 5 shows the position of the electrodes and the animal drawings show the dermatomes innervated by the fibres from each of those dermatomes.

FIG. 6 is a plot of ECAPs (fast responses) and slow responses, arising from stimulating at the top of the array. In this case three electrode leads were used to stimulate and measure. In the x-ray of FIG. 6, the top two electrode leads are placed in the normal direction (inserted in the rostral direction) whereas the bottom electrode lead was placed retrograde direction. The stimulus was at T13 and so the bottom electrode lead measures responses posterior (caudally) of the dermatome being stimulated. This is observed in the recording as a reversal in the polarity of the responses 630 relative to recordings 610 and 620. That is, the recordings obtained from electrodes E13 to E16 show a positive amplitude whereas the responses 610 and 620 from further up the cord show a negative response.

This demonstrates that the sign and shape of the slow response, being the peaks in the 3-5 ms range in FIG. 6, can be used to identify the location of the muscle group which is responding to the stimulus. The signal can be analysed in a number of different ways in order to extract information about the strength and source of the activation.

It is highly desirable in all neuromodulation applications which seek to affect a muscle group to achieve specificity i.e.

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selection of the targeted group and only that group. In the case of sacral nerve stimulation this is, according to theory, the detrusor muscle. Note that even if current theory is incorrect then it would also apply to other muscle groups for instance pelvic floor.

The present embodiment further provides for identification of the appropriate muscle group, by increasing the amplitude of the stimulation current, analysing the slow response, and identifying the slow response pattern which results. In this context it is to be understood that the slow response allows an understanding of muscle fibre activation to be derived from the late response in the neural measurements, providing similar information to electromyography (EMG).

Another property which is exploited by the present embodiment in identification of appropriate muscle groups is the fact that repetitive muscle fibre stimulation results in the fatigue of the muscle and loss of the slow response signal. In this regard, FIG. 7 shows the amplitude of both slow responses and fast responses (left panel) and the responses for two non-stimulating channels on the right panel. In this experiment the amplitude was increased and then held at 9 mA for two minutes. The amplitude of the response drops to zero as can be seen in the right panel as the muscle fatigues during the two minute period. Thus, an individual muscle group can be brought to fatigue with repetitive stimulation at a fixed amplitude. If the amplitude of the stimuli (or "shots" in FIG. 7) is further increased from this point then additional muscle fibres are recruited and even though responses from those that have fatigued are no longer observable new responses are evoked, as seen in FIG. 7 as the amplitude increases beyond the first fatigue point at 9 mA and the second fatigue point at 11 mA. In FIG. 8, note that the slow responses have a different morphology indicating some of the fibres are originating from an alternative muscle group location.

Identification of slow response patterns associated with muscle group activation, by measuring neural responses at or near the site of stimulation, is a matter of stimulating with an increase in amplitude over time and waiting at each selected current until the muscle group recruited at this stimulus level has fatigued, prior to the next step in current. Stimulation place perception or other measures of muscle group activation could be correlated with the response. In the case of the detrusor muscle this could be easily detected and correlated by using a catheter measuring the bladder pressure, for example. The bladder tends to respond to neural stimulation initially with rapid contraction followed by slow, longer-lasting relaxation. As the rapid contraction would only occur when the stimulus had reached the appropriate level to activate the detrusor muscle, then the slow response response derived from the neural observations could be determined by measurement of pressure change with a catheter. In this way the target pattern of slow responses for that muscle group can be determined by comparing observed slow responses to the catheter pressure results.

The above described staircase technique for filtering the responses can be used to determine the responses from individual groups of muscles. The contribution from all the fibres can then be compared with the sum of the responses obtained as the amplitude of stimulation is increased.

This technique has utility for any neural structure including spinal nerve roots. A further refinement can be made when the structure of a nerve bundle is considered. The individual fascicles in a nerve bundle meander through the length of the bundle as shown in FIG. 9, and so the

sensitivity of a particular fascicle to stimulation will change depending on the position along the length of the fibre. The technique described above could be used to determine the signature of the muscle group which is desired to be targeted and then the electrode and or position chosen to best recruit that fibre group.

The continuous measurement of the evoked response can be used as a feedback target in sacral nerve stimulation, whereby the stimulation should be set to achieve an absence of slow response or a small slow response after having fatigued the muscle. There are a number of ways to achieve this. The stimulation rate could be adjusted and a feedback algorithm used to control the inter stimulus interval such that a response is not generated. This is achieved by stimulating and measuring the response and if a slow response is present then shortening the time until the next stimuli. Over a much longer time scale, increments in the time between stimuli could be made so that the responses start to appear and this way the optimal stimulation rate is achieved. This process could be done at the time of programming or continuously in real time by the implant.

Referring to FIG. 10, the position of the nerve may change during the course of the therapy in particular for bladder control the filling of the bladder, bowels or patient movement would move the nerve within the sacral foramen and hence the efficacy of the stimulation would be altered as the nerve moves with respect to the electrode.

The fast response **510** is produced by the A β fibres and doesn't fatigue with stimulation in the same manner as the response from muscle groups. The A β response **510** also varies with amplitude depending on the distance of the responding fibre from the electrode. Thus, stimulation current adjustment for optimal motor fibre recruitment could be made on the basis of the amplitude of the A β response to account for movement of the nerve.

This change in stimulation current could be used to determine the state of the bladder, full or empty and further modifications made to the stimulus to account for this.

It will be appreciated by persons skilled in the art that numerous variations and/or modifications may be made to the invention as shown in the specific embodiments without departing from the spirit or scope of the invention as broadly described. The present embodiments are, therefore, to be considered in all respects as illustrative and not limiting or restrictive.

The invention claimed is:

1. A method of assessing a motor response to neural stimulation, the method comprising:

applying electrical stimuli from an electrode to a selected neural pathway to evoke an efferent neural response, the stimuli being configured to modulate motor activity;

measuring a slow neural response upon the neural pathway evoked by the electrical stimuli; and

based on the slow neural response, assessing a motor response of at least one muscle to the stimuli.

2. The method of claim **1**, when applied intra-operatively in order to use the measured slow response to locate the neural pathway and optimally position the electrode.

3. The method of claim **1**, further comprising applying stimuli at a first level for a period of time sufficient to fatigue a recruited portion of the associated muscle fibre population, and then applying stimuli at an increased level in order to recruit and assess a further portion of the muscle fibre population.

4. The method of claim **3** further comprising fatiguing the muscle fibres at various stimulus levels in order to explore characteristics of recruitment of each portion of the muscle fibre population.

5. The method of claim **1**, further comprising assessing a pattern or morphology of the slow response, to determine which muscle groups are being recruited by the stimulation.

6. The method of claim **1**, further comprising measuring a fast neural response to the stimuli, the fast response being the neural response observed in a time period of 0-2.5 ms after a stimulus.

7. The method of claim **1**, wherein the slow response comprises the neural response observed during a time period of 2-15 ms after a stimulus.

8. The method of claim **1**, wherein the stimulus is applied to preferentially evoke motor responses, to stimulate motor activity or suppress motor activity.

9. The method of claim **1** wherein the neural pathway comprises a sacral nerve.

10. The method of claim **1** wherein the neural pathway is used for gastric pacing.

11. The method of claim **1** wherein the neural pathway is used for functional electrical stimulation (FES).

12. The method of claim **1**, wherein the neural pathway is used for multifidus pacing.

13. A neurostimulator device comprising:

at least one stimulus electrode configured to be positioned adjacent to a neural pathway and to apply electrical stimuli to the neural pathway to evoke an efferent neural response, the stimuli being configured to modulate motor activity;

at least one sense electrode configured to be positioned adjacent to the neural pathway and to measure a slow neural response upon the neural pathway evoked by the electrical stimuli; and

a processor for assessing a motor response of at least one muscle to the stimuli, based on the slow neural response.

14. The neurostimulator device of claim **13**, configured to apply the electrical stimuli intra-operatively in order to use the measured slow response to locate the neural pathway and optimally position the electrode(s).

15. The neurostimulator device of claim **13**, wherein the processor is configured to further apply stimuli at a first level for a period of time sufficient to fatigue a recruited portion of muscle fibre population associated with the at least one muscle, and to then apply stimuli at an increased level in order to recruit and assess a further portion of the muscle fibre population.

16. The neurostimulator device of claim **15** wherein the processor is further configured to apply stimuli to fatigue the muscle fibre population at various stimulus levels in order to explore characteristics of recruitment of each portion of the muscle fibre population.

17. The neurostimulator device of claim **13**, wherein the processor is further configured to measure a fast neural response to the stimuli, the fast response being the neural response observed in a time period of 0-2.5 ms after a stimulus.

18. The neurostimulator device of claim **13**, wherein the slow response comprises the neural response observed during a time period of 2-15 ms after a stimulus.

19. The neurostimulator device of claim **13** wherein the processor is configured to apply a stimulus to preferentially evoke motor responses, to stimulate motor activity or suppress motor activity.